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(71) Applicant (for all designated States except US): **NOVARTIS AG** [CH/CH]; Lichtstrasse 35, CH-4056 Basel (CH).

(71) Applicant (for AT only): **NOVARTIS PHARMA GmbH** [AT/AT]; Brunner Strasse 59, A-1230 Vienna (AT).

(72) Inventor; and

(75) Inventor/Applicant (for US only): **BEBERNITZ, Gregory Raymond** [US/US]; 24 Lanes End, Stow, Massachusetts 01775 (US).

(74) Agent: **MILSTEAD, Mark, W.**; NOVARTIS, Corporate Intellectual Property, One Health Plaza Bldg. 104, East Hanover, New Jersey 07936 (US).

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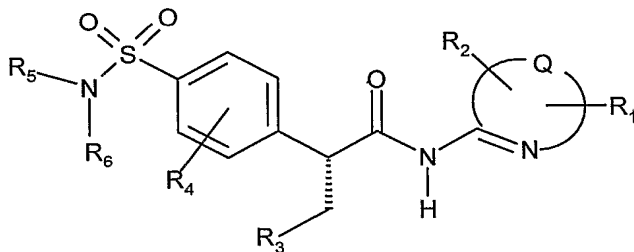
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(54) Title: ORGANIC COMPOUNDS



(I)

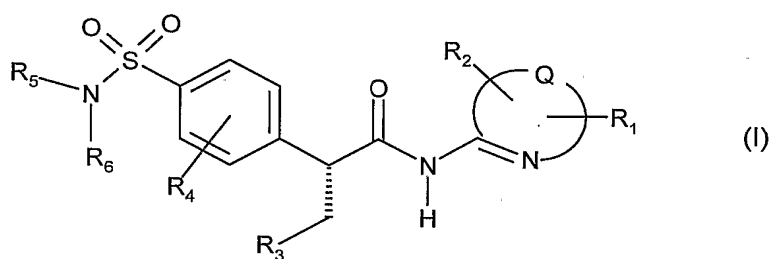
(57) Abstract: The present invention provides compounds of the formula (I); which are activators of glucokinase activity and, thus, may be employed as therapeutic agents for the treatment of glucokinase mediated conditions. Accordingly, the compounds of formula (I) may be employed for the prevention and the treatment of impaired glucose tolerance, type 2 diabetes and obesity.

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Organic Compounds

The present invention relates to certain sulfonamide derivatives, pharmaceutical compositions containing them, and to methods of treating glucokinase mediated conditions, in particular, impaired glucose tolerance and type 2 diabetes, by employing such compounds.

Accordingly, the present invention provides compounds of the formula



wherein

Q combined together with the carbon and nitrogen atoms to which it is attached form a 5- to 6-membered monocyclic heteroaromatic ring; or

Q combined together with the carbon and nitrogen atoms to which it is attached form a 9- to 10-membered bicyclic heterocycle;

R<sub>1</sub> and R<sub>2</sub> are, independently from each other, hydrogen, halogen, cyano, nitro, optionally substituted alkyl, alkoxy, alkylthio, alkylthiono, sulfonyl, free or esterified carboxy, carbamoyl, sulfamoyl, optionally substituted amino, aryl or heterocyclyl; or

R<sub>2</sub> is absent;

R<sub>3</sub> is C<sub>3</sub>-C<sub>6</sub> cycloalkyl or C<sub>3</sub>-C<sub>6</sub> heterocyclyl;

R<sub>4</sub> is hydrogen, halogen, cyano, lower alkyl or lower alkoxy;

R<sub>5</sub> is hydrogen, optionally substituted alkyl, or cycloalkyl;

R<sub>6</sub> is -(CR<sub>7</sub>R<sub>8</sub>)<sub>m</sub>-W-R<sub>9</sub> in which

R<sub>7</sub> and R<sub>8</sub> are, independently from each other, hydrogen, optionally substituted alkyl or cycloalkyl; or

R<sub>7</sub> and R<sub>8</sub> combined are alkylene which together with the carbon atom to which they are attached form a 3- to 7-membered ring;

m is zero or an integer from 1 to 5;

W is -NR<sub>10</sub>- in which

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R<sub>10</sub> is hydrogen, optionally substituted alkyl or heterocyclyl; or

R<sub>10</sub> is -C(O)R<sub>11</sub>, -C(O)OR<sub>11</sub>, or -C(O)NR<sub>12</sub>R<sub>13</sub> in which

R<sub>11</sub> and R<sub>12</sub> are, independently from each other, optionally substituted alkyl, cycloalkyl, aryl, heteroaryl, aralkyl or heteroaralkyl;

R<sub>13</sub> is hydrogen or lower alkyl; or

R<sub>13</sub> and R<sub>12</sub> combined are alkylene which together with the nitrogen atom to which they are attached form a 4- to 7-membered ring; or

W is absent;

R<sub>9</sub> is hydrogen, optionally substituted C<sub>1</sub>-C<sub>7</sub> alkyl, cycloalkyl, aryl or heterocyclyl; or

R<sub>9</sub> and R<sub>10</sub> combined are alkylene which together with the nitrogen atom to which they are attached form a 4- to 7-membered ring; or

R<sub>6</sub> and R<sub>5</sub> combined are alkylene which together with the nitrogen atom to which they are attached form a 4- to 7-membered ring which may be optionally substituted, or may contain 1 to 3 other heteroatoms selected from oxygen, nitrogen and sulfur, or may be part of another ring;

or an enantiomer thereof; or an enantiomeric mixture thereof; or a pharmaceutically acceptable salt thereof.

The compounds of the present invention provide pharmacological agents which are glucokinase activators and, thus, may be employed for the treatment of glucokinase mediated conditions. Accordingly, the compounds of formula (I) may be employed for prevention and treatment of impaired glucose tolerance, type 2 diabetes and obesity.

Listed below are definitions of various terms used to describe the compounds of the present invention. These definitions apply to the terms as they are used throughout the specification unless they are otherwise limited in specific instances either individually or as part of a larger group, , e.g., wherein an attachment point of a certain group is limited to a specific atom within that group, the point of attachment is defined by an arrow at the specific atom.

The term "optionally substituted alkyl" refers to unsubstituted or substituted alkyl groups, i.e., straight- or branched-chain hydrocarbon groups having 1-20 carbon atoms, preferably 1-10 carbon atoms. Exemplary unsubstituted alkyl groups include methyl, ethyl, propyl, isopropyl, *n*-butyl, *t*-butyl, isobutyl, pentyl, hexyl, isohexyl, heptyl, 4,4-dimethylpentyl, octyl and the like. Substituted alkyl groups include, but are not limited to, alkyl groups substituted by one or more of the following groups: halogen, hydroxy, alkanoyl, alkoxy, alkanoyloxy, thiol, alkylthio,

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alkylthiono, sulfonyl, sulfamoyl, carbamoyl, cyano, carboxy, acyl, aryl, alkenyl, alkynyl, aralkoxy, guanidino, optionally substituted amino, heterocyclyl including imidazolyl, furyl, thienyl, thiazolyl, pyrrolidyl, pyridyl, pyrimidyl and the like.

The term "lower alkyl" refers to those alkyl groups as described above having 1-7, preferably 2-4 carbon atoms.

The term "halogen" or "halo" refers to fluorine, chlorine, bromine and iodine.

The term "alkenyl" refers to any of the above alkyl groups having at least two carbon atoms and further containing a carbon to carbon double bond at the point of attachment. Groups having 2-4 carbon atoms are preferred.

The term "alkynyl" refers to any of the above alkyl groups having at least two carbon atoms and further containing a carbon to carbon triple bond at the point of attachment. Groups having 2-4 carbon atoms are preferred.

The term "alkylene" refers to a straight-chain bridge of 2-6 carbon atoms connected by single bonds, e.g.,  $-(CH_2)_x-$ , wherein x is 2-6, which may be interrupted with one or more heteroatoms selected from O, O-C(O)-, S, S(O), S(O)<sub>2</sub> or NR, wherein R may be hydrogen, alkyl, cycloalkyl, aryl, heterocyclyl, aralkyl, heteroaralkyl, acyl, carbamoyl, sulfonyl, alkoxycarbonyl, aryloxycarbonyl or aralkoxycarbonyl and the like. The alkylene may further be substituted with one or more substituents selected from optionally substituted alkyl, cycloalkyl, aryl, heterocyclyl, oxo, halogen, hydroxy, carboxy, alkoxy, alkoxycarbonyl and the like; and it may be part of another ring.

The term "cycloalkyl" refers to optionally substituted monocyclic, bicyclic or tricyclic hydrocarbon groups of 3-12 carbon atoms, each of which may contain one or more carbon to carbon double bonds, or the cycloalkyl may be substituted by one or more substituents, such as alkyl, halo, oxo, hydroxy, alkoxy, alkanoyl, acylamino, carbamoyl, alkylamino, dialkylamino, thiol, alkylthio, cyano, carboxy, alkoxycarbonyl, sulfonyl, sulfonamido, sulfamoyl, heterocyclyl and the like.

Exemplary monocyclic hydrocarbon groups include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclohexyl and cyclohexenyl and the like.

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Exemplary bicyclic hydrocarbon groups include bornyl, indyl, hexahydroindyl, tetrahydronaphthyl, decahydronaphthyl, bicyclo[2.1.1]hexyl, bicyclo[2.2.1]heptyl, bicyclo[2.2.1]heptenyl, 6,6-dimethylbicyclo[3.1.1]heptyl, 2,6,6-trimethylbicyclo[3.1.1]heptyl, bicyclo[2.2.2]octyl and the like.

Exemplary tricyclic hydrocarbon groups include adamantyl and the like.

The term "alkoxy" refers to alkyl-O-.

The term "alkanoyl" refers to alkyl-C(O)-.

The term "alkanoyloxy" refers to alkyl-C(O)-O-.

The terms "alkylamino" and "dialkylamino" refer to alkyl-NH- and (alkyl)<sub>2</sub>N-, respectively.

The term "alkanoylamino" refers to alkyl-C(O)-NH-.

The term "alkylthio" refers to alkyl-S-.

The term "trialkylsilyl" refers to (alkyl)<sub>3</sub>Si-.

The term "trialkylsilyloxy" refers to (alkyl)<sub>3</sub>SiO-.

The term "alkylthiono" refers to alkyl-S(O)-.

The term "alkylsulfonyl" refers to alkyl-S(O)<sub>2</sub>-.

The term "alkoxycarbonyl" refers to alkyl-O-C(O)-.

The term "alkoxycarbonyloxy" refers to alkyl-O-C(O)O-.

The term "carbamoyl" refers to H<sub>2</sub>NC(O)-, alkyl-NHC(O)-, (alkyl)<sub>2</sub>NC(O)-, aryl-NHC(O)-, alkyl(aryl)-NC(O)-, heteroaryl-NHC(O)-, alkyl(heteroaryl)-NC(O)-, aralkyl-NHC(O)-, alkyl(aralkyl)-NC(O)- and the like.

The term "sulfamoyl" refers to H<sub>2</sub>NS(O)<sub>2</sub>-, alkyl-NHS(O)<sub>2</sub>-, (alkyl)<sub>2</sub>NS(O)<sub>2</sub>-, aryl-NHS(O)<sub>2</sub>-, alkyl(aryl)-NS(O)<sub>2</sub>-, (aryl)<sub>2</sub>NS(O)<sub>2</sub>-, heteroaryl-NHS(O)<sub>2</sub>-, aralkyl-NHS(O)<sub>2</sub>-, heteroaralkyl-NHS(O)<sub>2</sub>- and the like.

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The term "sulfonamido" refers to alkyl-S(O)<sub>2</sub>-NH-, aryl-S(O)<sub>2</sub>-NH-, aralkyl-S(O)<sub>2</sub>-NH-, heteroaryl-S(O)<sub>2</sub>-NH-, heteroaralkyl-S(O)<sub>2</sub>-NH-, alkyl-S(O)<sub>2</sub>-N(alkyl)-, aryl-S(O)<sub>2</sub>-N(alkyl)-, aralkyl-S(O)<sub>2</sub>-N(alkyl)-, heteroaryl-S(O)<sub>2</sub>-N(alkyl)-, heteroaralkyl-S(O)<sub>2</sub>-N(alkyl)- and the like.

The term "sulfonyl" refers to alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aralkylsulfonyl, heteroaralkylsulfonyl and the like.

The term "optionally substituted amino" refers to an amino group which may optionally be substituted by substituents such as optionally substituted alkyl, acyl, sulfonyl, alkoxycarbonyl, cycloalkoxycarbonyl, aryloxycarbonyl, heteroaryloxycarbonyl, aralkoxycarbonyl, heteroaralkoxycarbonyl, carbamoyl and the like.

The term "aryl" refers to monocyclic or bicyclic aromatic hydrocarbon groups having 6-12 carbon atoms in the ring portion, such as phenyl, biphenyl, naphthyl and tetrahydronaphthyl, each of which may optionally be substituted by 1-4 substituents, such as optionally substituted alkyl, trifluoromethyl, cycloalkyl, halo, hydroxy, alkoxy, acyl, alkanoyloxy, aryloxy, optionally substituted amino, thiol, alkylthio, arylthio, nitro, cyano, carboxy, alkoxycarbonyl, carbamoyl, alkylthiono, sulfonyl, sulfonamido, heterocyclyl and the like.

The term "monocyclic aryl" refers to optionally substituted phenyl as described under aryl.

The term "aralkyl" refers to an aryl group bonded directly through an alkyl group, such as benzyl.

The term "aralkanoyl" refers to aralkyl-C(O)-.

The term "aralkylthio" refers to aralkyl-S-.

The term "aralkoxy" refers to an aryl group bonded directly through an alkoxy group.

The term "arylsulfonyl" refers to aryl-S(O)<sub>2</sub>-.

The term "arylthio" refers to aryl-S-.

The term "aroyl" refers to aryl-C(O)-.

The term "aroyloxy" refers to aryl-C(O)-O-.

The term "aroylamino" refers to aryl-C(O)-NH-.

The term "aryloxycarbonyl" refers to aryl-O-C(O)-.

The term "heterocyclyl" or "heterocyclo" refers to an optionally substituted, fully saturated or unsaturated, aromatic or nonaromatic cyclic group, e.g., which is a 4- to 7-membered monocyclic, 7- to 12-membered bicyclic or 10- to 15-membered tricyclic ring system, which has at least one heteroatom in at least one carbon atom-containing ring. Each ring of the heterocyclic group containing a heteroatom may have 1, 2 or 3 heteroatoms selected from nitrogen atoms, oxygen atoms and sulfur atoms, where the nitrogen and sulfur heteroatoms may also optionally be oxidized. The heterocyclic group may be attached at a heteroatom or a carbon atom.

Exemplary monocyclic heterocyclic groups include pyrrolidinyl, pyrrolyl, pyrazolyl, oxetanyl, pyrazolinyl, imidazolyl, imidazolynyl, imidazolidinyl, triazolyl, oxazolyl, oxazolidinyl, isoxazolinyl, isoxazolyl, thiazolyl, thiadiazolyl, thiazolidinyl, isothiazolyl, isothiazolidinyl, furyl, tetrahydrofuryl, thienyl, oxadiazolyl, piperidinyl, piperazinyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolodinyl, 2-oxoazepinyl, azepinyl, 4-piperidonyl, pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl, tetrahydropyranyl, morpholinyl, thiamorpholinyl, thiamorpholinyl sulfoxide, thiamorpholinyl sulfone, 1,3-dioxolane and tetrahydro-1,1-dioxothienyl, 1,1,4-trioxo-1,2,5-thiadiazolidin-2-yl and the like.

Exemplary bicyclic heterocyclic groups include indolyl, dihydroidolyl, benzothiazolyl, 4,5,6,7-tetrahydro-benzothiazolyl, benzoxazinyl, benzoxazolyl, benzothienyl, benzothiazinyl, thiazolo[5,4-b]pyridinyl, thiazolo[5,4-d]pyrimidinyl, oxazolo[5,4-b]pyridinyl, 6,7-dihydro-4H-thiopyrano[4,3-d]thiazolyl, 6,7-dihydro-4H-pyrano[4,3-d]thiazolyl, 4,5,6,7-tetrahydro-thiazolo[5,4-c]pyridinyl, 4,5,6,7-tetrahydro-pyrazolo[1,5-a]pyridinyl, 5,6,7,8-tetrahydro-triazolo[1,5-a]pyridinyl, quinuclidinyl, quinolinyl, tetrahydroquinolinyl, decahydroquinolinyl, isoquinolinyl, tetrahydroisoquinolinyl, decahydroisoquinolinyl, benzimidazolyl, benzopyranyl, indolizinyl, benzofuryl, chromonyl, coumarinyl, benzopyranyl, cinnolinyl, quinoxalinyl, indazolyl, pyrrolopyridyl, furopyridinyl (such as furo[2,3-c]pyridinyl, furo[3,2-b]-pyridinyl] or furo[2,3-b]pyridinyl), dihydroisoindolyl, 1,3-dioxo-1,3-dihydroisoindol-2-yl, dihydroquinazolinyl (such as 3,4-dihydro-4-oxo-quinazolinyl), phthalazinyl and the like.

Exemplary tricyclic heterocyclic groups include carbazolyl, dibenzoazepinyl, dithienoazepinyl, benzindolyl, phenanthrolinyl, acridinyl, phenanthridinyl, phenoxazinyl, phenothiazinyl, xanthenyl, carbolinyl and the like.

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The term "heterocyclyl" includes substituted heterocyclic groups. Substituted heterocyclic groups refer to heterocyclic groups substituted with 1, 2 or 3 substituents selected from the group consisting of the following:

- (a) optionally substituted alkyl;
- (b) hydroxyl (or protected hydroxyl);
- (c) halo;
- (d) oxo, i.e., =O;
- (e) optionally substituted amino;
- (f) alkoxy;
- (g) cycloalkyl;
- (h) free or esterified carboxy;
- (i) heterocyclyl;
- (j) alkylthio;
- (k) alkylthiono;
- (l) nitro;
- (m) cyano;
- (n) sulfamoyl;
- (o) alkanoyloxy;
- (p) aroyloxy;
- (q) arylthio;
- (r) aryloxy;
- (s) sulfamoyl;
- (t) sulfonyl;
- (u) carbamoyl;
- (v) aralkyl; and
- (w) aryl optionally substituted with alkyl, cycloalkyl, alkoxy, hydroxyl, amino, acylamino, alkylamino, dialkylamino or halo.

The term "heterocyclooxy" denotes a heterocyclic group bonded through an oxygen bridge.

The term "heteroaryl" refers to an aromatic heterocycle, e.g., monocyclic or bicyclic aryl, such as pyrrolyl, pyrazolyl, imidazolyl, triazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, furyl, thienyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, indolyl, benzothiazolyl, benzoxazolyl, benzothienyl, quinolinyl, isoquinolinyl, benzimidazolyl, benzofuryl and the like, optionally substituted by, e.g., lower alkyl, lower alkoxy or halo.



The term "heteroarylsulfonyl" refers to heteroaryl-S(O)<sub>2</sub>-.

The term "heteroaroyl" refers to heteroaryl-C(O)-.

The term "heteroaryloxycarbonyl" refers to heteroaryl-O-C(O)-.

The term "heteroaroylamino" refers to heteroaryl-C(O)NH-.

The term "heteroaralkyl" refers to a heteroaryl group bonded through an alkyl group.

The term "heteroaralkanoyl" refers to heteroaralkyl-C(O)-.

The term "heteroaralkanoylamino" refers to heteroaralkyl-C(O)NH-.

The term "acyl" refers to alkanoyl, aroyl, heteroaroyl, aralkanoyl, heteroaralkanoyl and the like.

The term "acylamino" refers to alkanoylamino, aroylamino, heteroaroylamino, aralkanoylamino, heteroaralkanoylamino and the like.

The term "esterified carboxy" refers to optionally substituted alkoxycarbonyl, cycloalkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, heterocyclooxycarbonyl and the like.

Pharmaceutically acceptable salts of the compounds of the present invention refer to salts formed with acids, namely acid addition salts, such as of mineral acids, organic carboxylic acids and organic sulfonic acids, e.g., hydrochloric acid, maleic acid and methanesulfonic acid, respectively.

Similarly, pharmaceutically acceptable salts of the compounds of the invention refer to salts formed with bases, namely cationic salts, such as alkali and alkaline earth metal salts, e.g., sodium, lithium, potassium, calcium and magnesium, as well as ammonium salts, e.g., ammonium, trimethylammonium, diethylammonium and tris(hydroxymethyl)-methylammonium salts and salts with amino acids provided an acidic group constitutes part of the structure.

As described herein above, the present invention provides certain sulfonamide derivatives of formula (I), pharmaceutical compositions containing them, methods for preparing said compounds, and methods of treating glucokinase mediated conditions by administration of a

therapeutically effective amount of a compound of the present invention, or a pharmaceutical composition thereof.

Preferred are the compounds of formula (I), designated as the A group, wherein

$R_1$  and  $R_2$  are, independently from each other, hydrogen, halogen, cyano, nitro, optionally substituted alkyl, alkoxy, alkylthio, alkylthiono, sulfonyl, free or esterified carboxy, carbamoyl, sulfamoyl, optionally substituted amino, aryl or heterocyclyl; or

$R_2$  is absent;

$R_3$  is cyclopentyl;

$R_4$  is hydrogen;

$R_5$  is hydrogen or lower alkyl;

$R_6$  is  $-(CR_7R_8)_m-W-R_9$  in which

$R_7$  and  $R_8$  are independently hydrogen or optionally substituted lower alkyl;

$m$  is zero or an integer from 1 to 5;

$W$  is  $-NR_{10}-$  in which

$R_{10}$  is hydrogen or lower alkyl; or

$R_{10}$  is  $-C(O)R_{11}$ ,  $-C(O)OR_{11}$ , or  $-C(O)NR_{12}R_{13}$  in which

$R_{11}$  and  $R_{12}$  are, independently from each other, optionally substituted alkyl, cycloalkyl, aryl, heteroaryl, aralkyl or heteroaralkyl;

$R_{13}$  is hydrogen or lower alkyl; or

$R_{13}$  and  $R_{12}$  combined are alkylene which together with the nitrogen atom to which they are attached form a 5- to 7-membered ring; or

$W$  is absent;

$R_9$  is hydrogen, optionally substituted  $C_1$ - $C_7$  alkyl, cycloalkyl, aryl or heterocyclyl; or

$R_9$  and  $R_{10}$  combined are alkylene which together with the nitrogen atom to which they are attached form a 5- to 7-membered ring; or

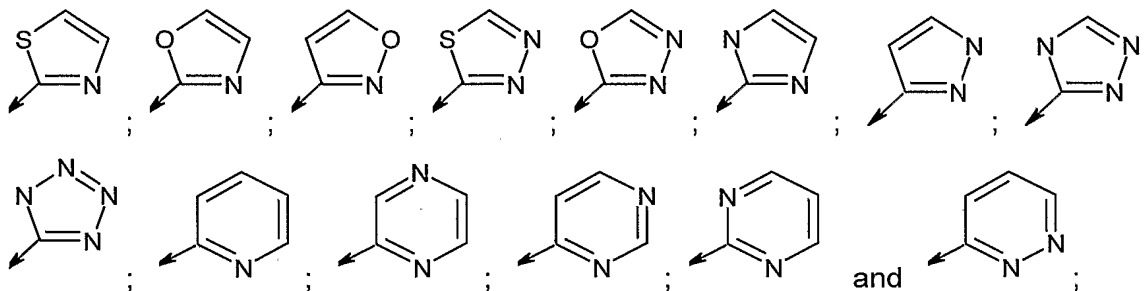
$R_6$  and  $R_5$  combined are alkylene which together with the nitrogen atom to which they are attached form a 4- to 7-membered ring which may be optionally substituted, or may contain 1 to 3 other heteroatoms selected from oxygen, nitrogen and sulfur, or may be part of another ring;

or an enantiomer thereof; or an enantiomeric mixture thereof; or a pharmaceutically acceptable salt thereof.

Preferred are the compounds in the A group, designated as the B group, wherein

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Q combined together with the carbon and nitrogen atoms to which it is attached form a 5- to 6-membered monocyclic heteroaromatic ring which is selected from the group consisting of



$R_5$  is hydrogen or lower alkyl;

$R_6$  is  $-(CR_7R_8)_m-W-R_9$  in which

$R_7$  and  $R_8$  are hydrogen;

$m$  is an integer from 2 to 5;

$W$  is  $-NR_{10}-$  in which

$R_{10}$  is hydrogen or lower alkyl; or

$R_{10}$  is  $-C(O)R_{11}$ ,  $-C(O)OR_{11}$ , or  $-C(O)NR_{12}R_{13}$  in which

$R_{11}$  and  $R_{12}$  are, independently from each other, optionally substituted alkyl, cycloalkyl, aryl, heteroaryl, aralkyl or heteroaralkyl;

$R_{13}$  is hydrogen or lower alkyl; or

$R_{13}$  and  $R_{12}$  combined are alkylene which together with the nitrogen atom to which they are attached form a 5- to 7-membered ring; or

$W$  is absent;

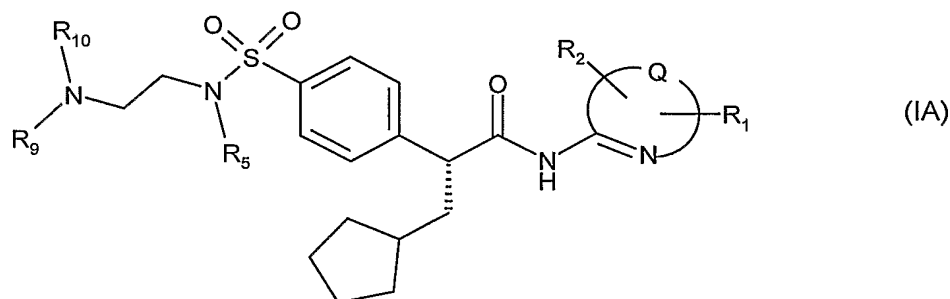
$R_9$  is hydrogen, optionally substituted  $C_1$ - $C_7$  alkyl, cycloalkyl, aryl or heterocyclyl; or

$R_9$  and  $R_{10}$  combined are alkylene which together with the nitrogen atom to which they are attached form a 5- to 7-membered ring;

or an enantiomer thereof; or an enantiomeric mixture thereof; or a pharmaceutically acceptable salt thereof.

Preferred are the compounds in the B group having the formula

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wherein

$\text{R}_1$  is hydrogen, halogen, cyano, trifluoromethyl, alkoxy, alkylthio or carboxy;

$\text{R}_2$  is absent;

$\text{R}_5$  is hydrogen or lower alkyl;

$\text{R}_9$  is hydrogen, optionally substituted  $\text{C}_1\text{-C}_7$  alkyl, cycloalkyl, aryl or heterocyclyl;

$\text{R}_{10}$  is hydrogen or lower alkyl; or

$\text{R}_{10}$  is  $-\text{C}(\text{O})\text{R}_{11}$ ,  $-\text{C}(\text{O})\text{OR}_{11}$ , or  $-\text{C}(\text{O})\text{NR}_{12}\text{R}_{13}$  in which

$\text{R}_{11}$  and  $\text{R}_{12}$  are, independently from each other, optionally substituted alkyl, cycloalkyl, aryl, heteroaryl, aralkyl or heteroaralkyl;

$\text{R}_{13}$  is hydrogen or lower alkyl; or

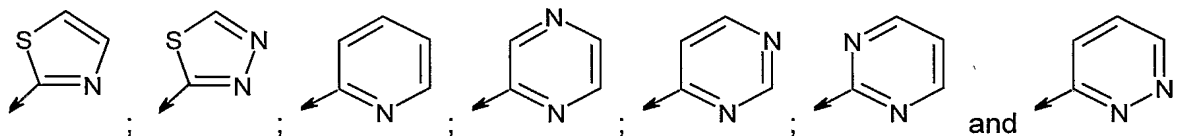
$\text{R}_{13}$  and  $\text{R}_{12}$  combined are alkylene which together with the nitrogen atom to which they are attached form a 5- to 7-membered ring; or

$\text{R}_{10}$  and  $\text{R}_9$  combined are alkylene which together with the nitrogen atom to which they are attached form a 5- to 7-membered ring;

or an enantiomer thereof; or an enantiomeric mixture thereof; or a pharmaceutically acceptable salt thereof.

Preferred are the compounds of formula (IA) in the B group wherein

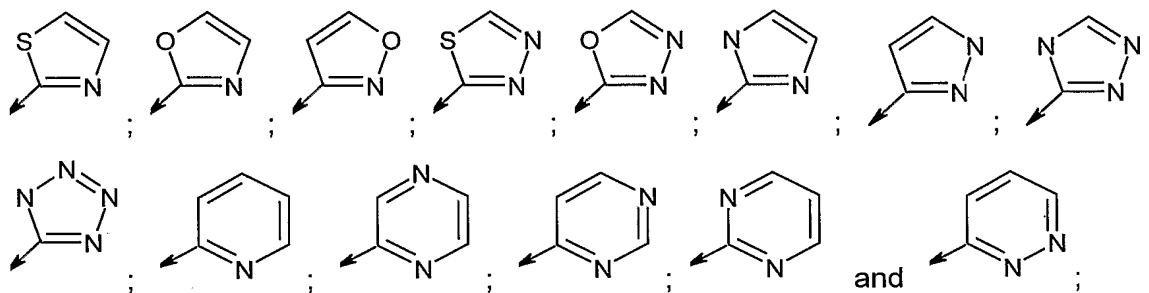
$\text{Q}$  combined together with the carbon and nitrogen atoms to which it is attached form a 5- to 6-membered monocyclic heteroaromatic ring which is selected from the group consisting of



or an enantiomer thereof; or an enantiomeric mixture thereof; or a pharmaceutically acceptable salt thereof.

Preferred are also the compounds in the A group, designated as the C group, wherein

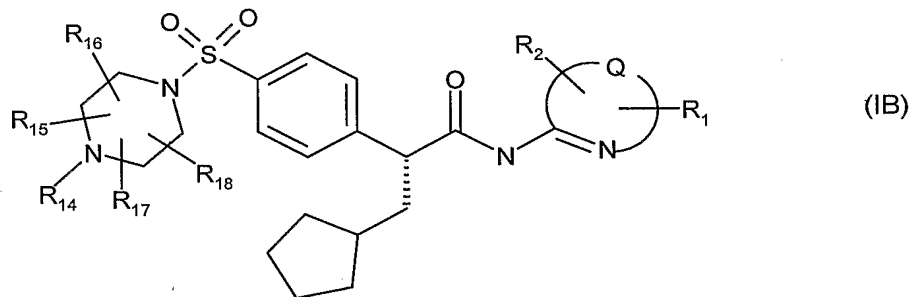
Q combined together with the carbon and nitrogen atoms to which it is attached form a 5- to 6-membered monocyclic heteroaromatic ring which is selected from the group consisting of



$R_6$  and  $R_5$  combined are alkylene which together with the nitrogen atom to which they are attached form a 4- to 7-membered ring which may be optionally substituted, or may contain 1 to 3 other heteroatoms selected from oxygen, nitrogen and sulfur, or may be part of another ring;

or an enantiomer thereof; or an enantiomeric mixture thereof; or a pharmaceutically acceptable salt thereof.

Preferred are the compounds in the C group having the formula



wherein

$R_1$  is hydrogen, halogen, cyano, trifluoromethyl, alkoxy, alkylthio or carboxy;

$R_2$  is absent;

$R_{14}$  is hydrogen, optionally substituted lower alkyl, cycloalkyl, aryl, heteroaryl, aralkyl or heteroaralkyl; or

$R_{14}$  is  $-C(O)R_{19}$ ,  $-C(O)OR_{19}$ , or  $-C(O)NR_{20}R_{21}$  in which

$R_{19}$  and  $R_{20}$  are, independently from each other, optionally substituted alkyl, cycloalkyl, aryl, heteroaryl, aralkyl or heteroaralkyl;

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$R_{21}$  is hydrogen or lower alkyl; or

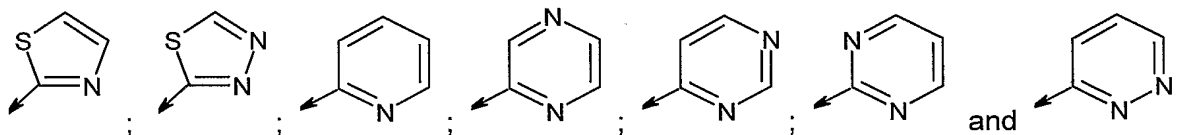
$R_{21}$  and  $R_{20}$  combined are alkylene which together with the nitrogen atom to which they are attached form a 5- to 7-membered ring;

$R_{15}$ ,  $R_{16}$ ,  $R_{17}$  and  $R_{18}$  are, independently from each other, hydrogen, halogen, hydroxy, alkoxy, free or esterified carboxy, optionally substituted lower alkyl, cycloalkyl, aryl, aralkyl, heteroaralkyl or heterocyclyl;

or an enantiomer thereof; or an enantiomeric mixture thereof; or a pharmaceutically acceptable salt thereof.

Preferred are the compounds of formula (IB) in the C group wherein

Q combined together with the carbon and nitrogen atoms to which it is attached form a 5- to 6-membered monocyclic heteroaromatic ring which is selected from the group consisting of



or an enantiomer thereof; or an enantiomeric mixture thereof; or a pharmaceutically acceptable salt thereof.

Further preferred are the compounds of formula (IB) in the C group wherein

$R_{14}$  is methyl;

or an enantiomer thereof; or an enantiomeric mixture thereof; or a pharmaceutically acceptable salt thereof.

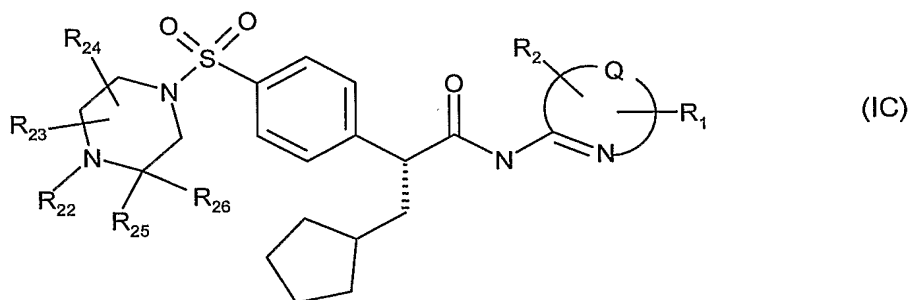
Further preferred are also the compounds of formula (IB) in the C group wherein

$R_{14}$ ,  $R_{15}$ ,  $R_{16}$ ,  $R_{17}$  and  $R_{18}$  are, independently from each other, hydrogen or methyl;

or an enantiomer thereof; or an enantiomeric mixture thereof; or a pharmaceutically acceptable salt thereof.

Preferred are also the compounds in the C group having the formula

- 14 -



wherein

R<sub>1</sub> is hydrogen, halogen, cyano, trifluoromethyl, alkoxy, alkylthio or carboxy;

R<sub>2</sub> is absent;

R<sub>22</sub> is hydrogen, optionally substituted lower alkyl, cycloalkyl, aryl, heteroaryl, aralkyl or heteroaralkyl; or

R<sub>22</sub> is -C(O)R<sub>19</sub>, -C(O)OR<sub>19</sub>, or -C(O)NR<sub>20</sub>R<sub>21</sub> in which

R<sub>19</sub> and R<sub>20</sub> are, independently from each other, optionally substituted alkyl, cycloalkyl, aryl, heteroaryl, aralkyl or heteroaralkyl;

R<sub>21</sub> is hydrogen or lower alkyl; or

R<sub>21</sub> and R<sub>20</sub> combined are alkylene which together with the nitrogen atom to which they are attached form a 5- to 7-membered ring;

R<sub>23</sub>, R<sub>24</sub>, R<sub>25</sub> and R<sub>26</sub> are, independently from each other, hydrogen, halogen, hydroxy, alkoxy, free or esterified carboxy, optionally substituted lower alkyl, cycloalkyl, aryl, aralkyl, heteroaralkyl or heterocyclyl; or

R<sub>22</sub> and R<sub>25</sub> combined are alkylene which together with the nitrogen and carbon atoms to which they are attached form a 4- to 7-membered ring; or

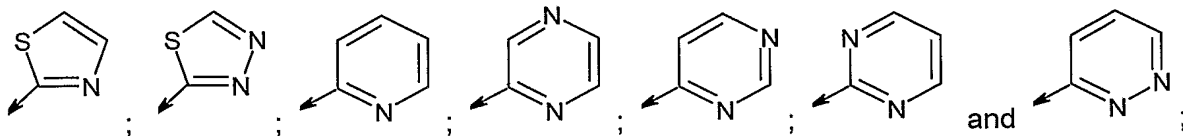
R<sub>25</sub> and R<sub>26</sub> combined are alkylene which together with the carbon atom to which they are attached form a 3- to 7-membered ring;

or an enantiomer thereof; or an enantiomeric mixture thereof; or a pharmaceutically acceptable salt thereof.

Preferred are the compounds of formula (IC) in the C group wherein

Q combined together with the carbon and nitrogen atoms to which it is attached form a 5- to 6-membered monocyclic heteroaromatic ring which is selected from the group consisting of

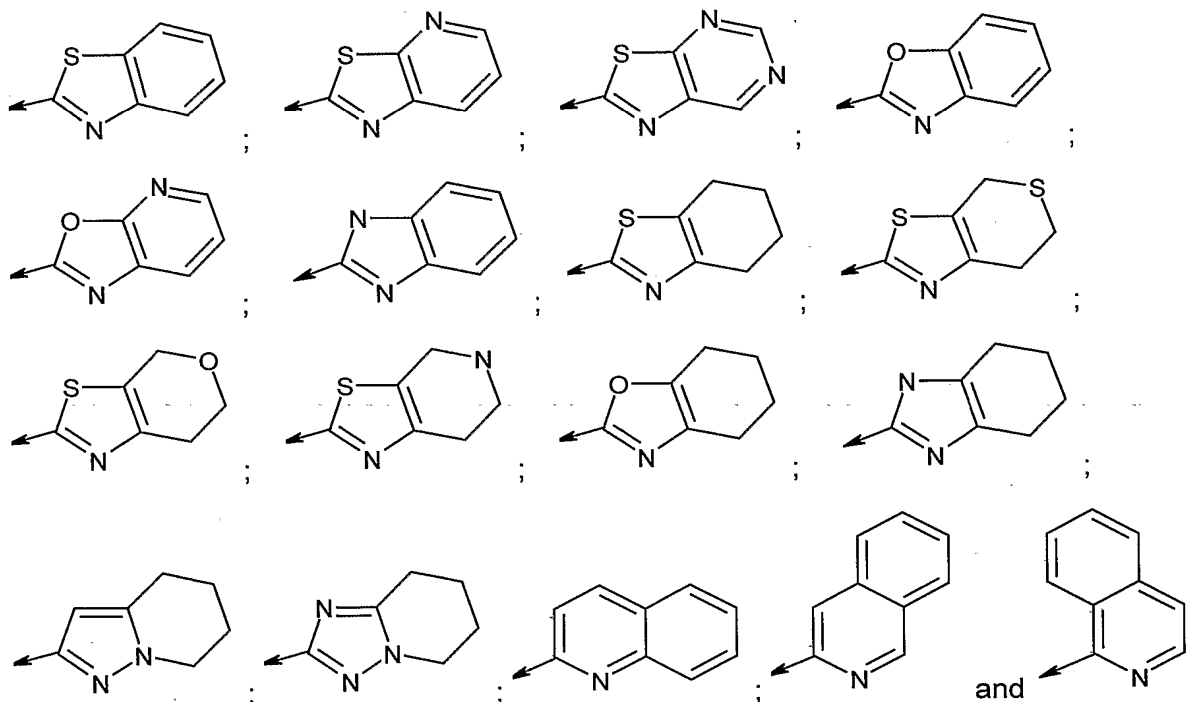
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or an enantiomer thereof; or an enantiomeric mixture thereof; or a pharmaceutically acceptable salt thereof.

Preferred are also the compounds in the A group, designated as the D group, wherein

Q combined together with the carbon and nitrogen atoms to which it is attached form a 9- to 10-membered bicyclic heterocycle which is selected from the group consisting of



$R_5$  is hydrogen or lower alkyl;

$R_6$  is  $-(CR_7R_8)_m-W-R_9$  in which

$R_7$  and  $R_8$  are hydrogen;

$m$  is an integer from 2 to 5;

$W$  is  $-NR_{10}-$  in which

$R_{10}$  is hydrogen or lower alkyl; or

$R_{10}$  is  $-C(O)R_{11}$ ,  $-C(O)OR_{11}$ , or  $-C(O)NR_{12}R_{13}$  in which

$R_{11}$  and  $R_{12}$  are, independently from each other, optionally substituted alkyl, cycloalkyl, aryl, heteroaryl, aralkyl or heteroaralkyl;

$R_{13}$  is hydrogen or lower alkyl; or



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$R_{13}$  and  $R_{12}$  combined are alkylene which together with the nitrogen atom to which they are attached form a 5- to 7-membered ring; or

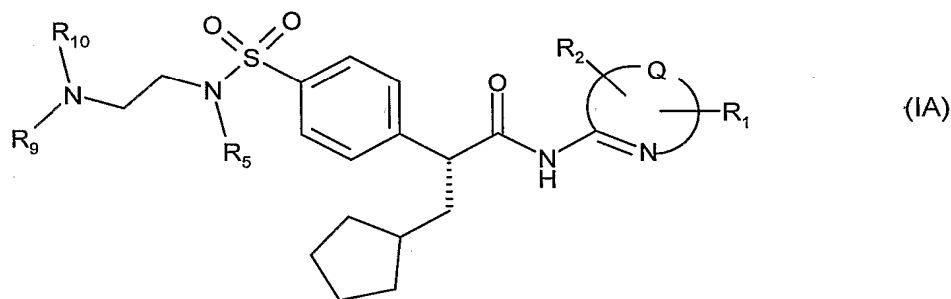
W is absent;

$R_9$  is hydrogen, optionally substituted  $C_1$ - $C_7$  alkyl, cycloalkyl, aryl or heterocyclyl; or

$R_9$  and  $R_{10}$  combined are alkylene which together with the nitrogen atom to which they are attached form a 5- to 7-membered ring;

or an enantiomer thereof; or an enantiomeric mixture thereof; or a pharmaceutically acceptable salt thereof.

Preferred are the compounds in the D group having the formula



wherein

$R_1$  is hydrogen, halogen, cyano, trifluoromethyl, alkoxy, alkylthio or carboxy;

$R_2$  is absent;

$R_5$  is hydrogen or lower alkyl;

$R_9$  is hydrogen, optionally substituted  $C_1$ - $C_7$  alkyl, cycloalkyl, aryl or heterocyclyl;

$R_{10}$  is hydrogen or lower alkyl; or

$R_{10}$  is  $-C(O)R_{11}$ ,  $-C(O)OR_{11}$ , or  $-C(O)NR_{12}R_{13}$  in which

$R_{11}$  and  $R_{12}$  are, independently from each other, optionally substituted alkyl, cycloalkyl, aryl, heteroaryl, aralkyl or heteroaralkyl;

$R_{13}$  is hydrogen or lower alkyl; or

$R_{13}$  and  $R_{12}$  combined are alkylene which together with the nitrogen atom to which they are attached form a 5- to 7-membered ring; or

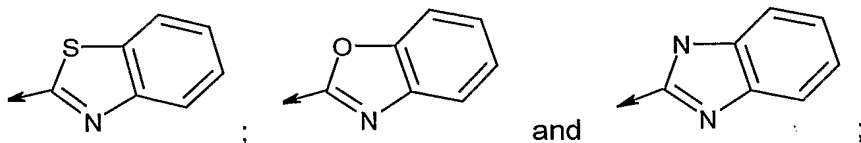
$R_{10}$  and  $R_9$  combined are alkylene which together with the nitrogen atom to which they are attached form a 5- to 7-membered ring;

or an enantiomer thereof; or an enantiomeric mixture thereof; or a pharmaceutically acceptable salt thereof.

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Preferred are the compounds of formula (IA) in the D group wherein

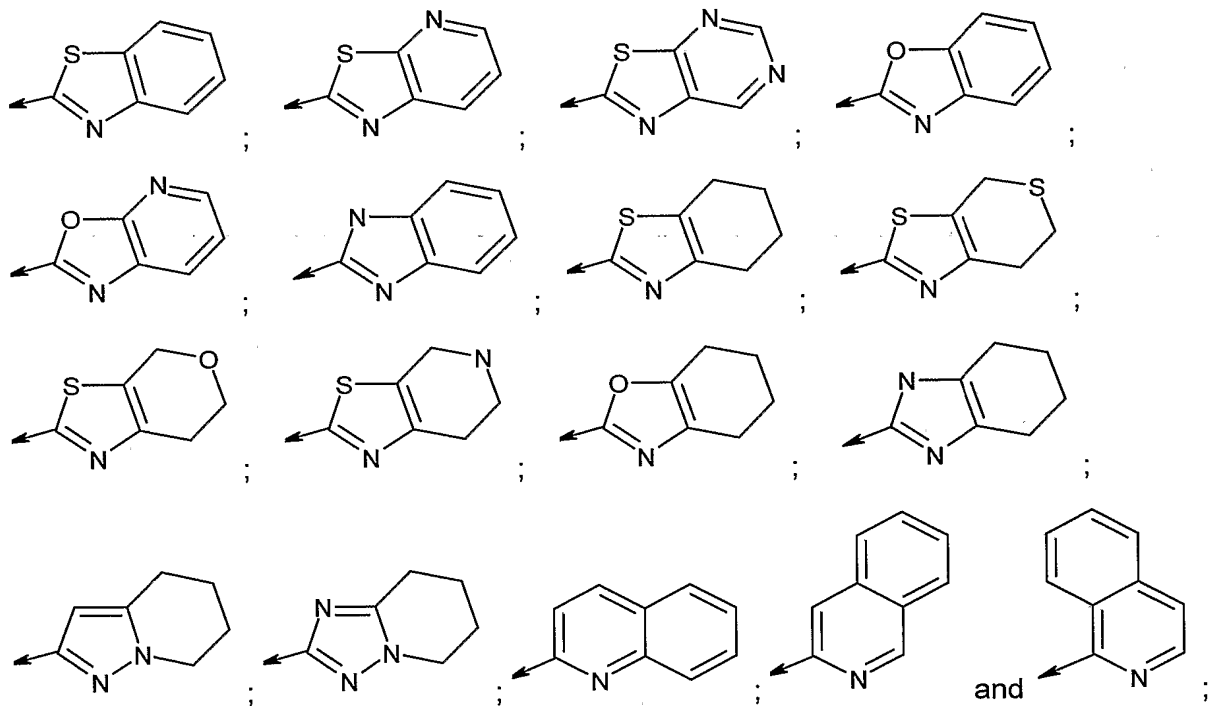
Q combined together with the carbon and nitrogen atoms to which it is attached form a 9- to 10-membered bicyclic heterocycle which is selected from the group consisting of



or an enantiomer thereof; or an enantiomeric mixture thereof; or a pharmaceutically acceptable salt thereof.

Preferred are also the compounds in the A group, designated as the E group, wherein

Q combined together with the carbon and nitrogen atoms to which it is attached form a 9- to 10-membered bicyclic heterocycle which is selected from the group consisting of

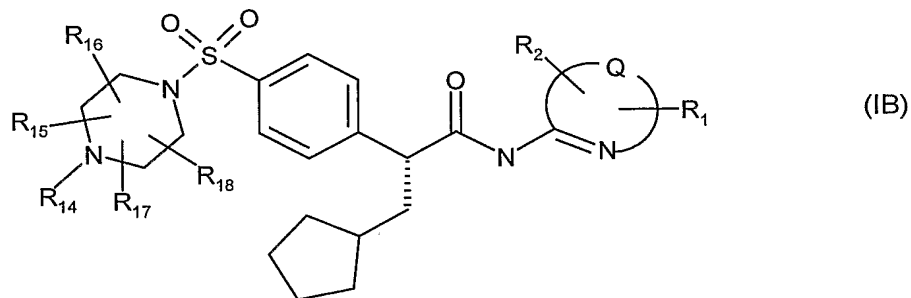


$R_6$  and  $R_5$  combined are alkylene which together with the nitrogen atom to which they are attached form a 4- to 7-membered ring which may be optionally substituted, or may contain 1 to 3 other heteroatoms selected from oxygen, nitrogen and sulfur, or may be part of another ring;

or an enantiomer thereof; or an enantiomeric mixture thereof; or a pharmaceutically acceptable salt thereof.

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Preferred are the compounds in the E group having the formula



wherein

$R_1$  is hydrogen, halogen, cyano, trifluoromethyl, alkoxy, alkylthio or carboxy;

$R_2$  is absent;

$R_{14}$  is hydrogen, optionally substituted lower alkyl, cycloalkyl, aryl, heteroaryl, aralkyl or heteroaralkyl; or

$R_{14}$  is  $-C(O)R_{19}$ ,  $-C(O)OR_{19}$ , or  $-C(O)NR_{20}R_{21}$  in which

$R_{19}$  and  $R_{20}$  are, independently from each other, optionally substituted alkyl, cycloalkyl, aryl, heteroaryl, aralkyl or heteroaralkyl;

$R_{21}$  is hydrogen or lower alkyl; or

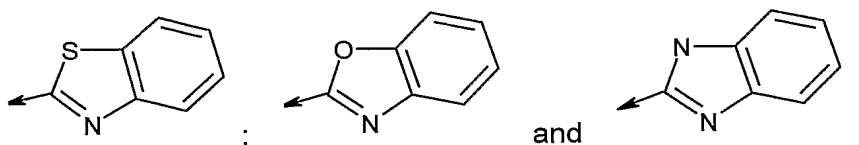
$R_{21}$  and  $R_{20}$  combined are alkylene which together with the nitrogen atom to which they are attached form a 5- to 7-membered ring;

$R_{15}$ ,  $R_{16}$ ,  $R_{17}$  and  $R_{18}$  are, independently from each other, hydrogen, halogen, hydroxy, alkoxy, free or esterified carboxy, optionally substituted lower alkyl, cycloalkyl, aryl, aralkyl, heteroaralkyl or heterocyclyl;

or an enantiomer thereof; or an enantiomeric mixture thereof; or a pharmaceutically acceptable salt thereof.

Preferred are the compounds of formula (IB) in the E group wherein

Q combined together with the carbon and nitrogen atoms to which it is attached form a 9- to 10-membered bicyclic heterocycle which is selected from the group consisting of



or an enantiomer thereof; or an enantiomeric mixture thereof; or a pharmaceutically acceptable salt thereof.

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Further preferred are the compounds of formula (IB) in the E group wherein

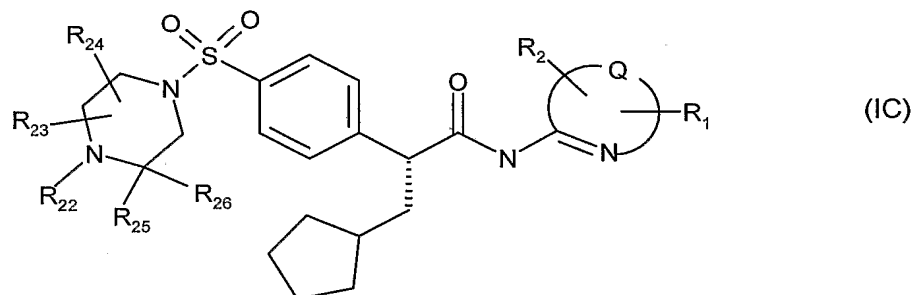
$R_{14}$  is methyl;

or an enantiomer thereof; or an enantiomeric mixture thereof; or a pharmaceutically acceptable salt thereof.

Further preferred are also the compounds of formula (IB) in the E group wherein

$R_{14}$ ,  $R_{15}$ ,  $R_{16}$ ,  $R_{17}$  and  $R_{18}$  are, independently from each other, hydrogen or methyl; or an enantiomer thereof; or an enantiomeric mixture thereof; or a pharmaceutically acceptable salt thereof.

Preferred are also the compounds in the E group having the formula



wherein

$R_1$  is hydrogen, halogen, cyano, trifluoromethyl, alkoxy, alkylthio or carboxy;

$R_2$  is absent;

$R_{22}$  is hydrogen, optionally substituted lower alkyl, cycloalkyl, aryl, heteroaryl, aralkyl or heteroaralkyl; or

$R_{22}$  is  $-C(O)R_{19}$ ,  $-C(O)OR_{19}$ , or  $-C(O)NR_{20}R_{21}$  in which

$R_{19}$  and  $R_{20}$  are, independently from each other, optionally substituted alkyl, cycloalkyl, aryl, heteroaryl, aralkyl or heteroaralkyl;

$R_{21}$  is hydrogen or lower alkyl; or

$R_{21}$  and  $R_{20}$  combined are alkylene which together with the nitrogen atom to which they are attached form a 5- to 7-membered ring;

$R_{23}$ ,  $R_{24}$ ,  $R_{25}$  and  $R_{26}$  are, independently from each other, hydrogen, halogen, hydroxy, alkoxy, free or esterified carboxy, optionally substituted lower alkyl, cycloalkyl, aryl, aralkyl, heteroaralkyl or heterocyclyl; or

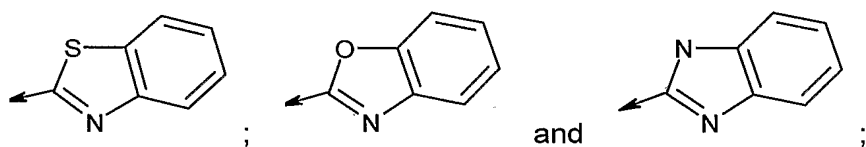
$R_{22}$  and  $R_{25}$  combined are alkylene which together with the nitrogen and carbon atoms to which they are attached form a 4- to 7-membered ring; or

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$R_{25}$  and  $R_{26}$  combined are alkylene which together with the carbon atom to which they are attached form a 3- to 7-membered ring;  
or an enantiomer thereof; or an enantiomeric mixture thereof; or a pharmaceutically acceptable salt thereof.

Preferred are the compounds of formula (IC) in the E group wherein

Q combined together with the carbon and nitrogen atoms to which it is attached form a 9- to 10-membered bicyclic heterocycle which is selected from the group consisting of



or an enantiomer thereof; or an enantiomeric mixture thereof; or a pharmaceutically acceptable salt thereof.

The compounds of the invention depending on the nature of the substituents possess one or more asymmetric centers. The resulting diastereoisomers, optical isomers, i.e., enantiomers, and geometric isomers, and mixtures thereof, are encompassed by the instant invention. Preferred are the compounds of the present invention wherein the substituent at the carbon atom adjacent to the amide group attains the R-configuration.

Particular embodiments of the invention are:

3-Cyclopentyl-N-isoquinolin-1-yl-2-[4-(4-methyl-piperazine-1-sulfonyl)-phenyl]-propionamide;

3-Cyclopentyl-N-(1-methyl-1H-benzimidazol-2-yl)-2-[4-(4-methyl-piperazine-1-sulfonyl)-phenyl]-propionamide;

3-Cyclopentyl-2-[4-(4-methyl-piperazine-1-sulfonyl)-phenyl]-N-[1,3,4]thiadiazol-2-yl-propionamide;

3-Cyclopentyl-2-[4-(4-methyl-piperazine-1-sulfonyl)-phenyl]-N-quinolin-2-yl-propionamide;

N-(6-Chloro-pyridazin-3-yl)-3-cyclopentyl-2-[4-(4-methyl-piperazine-1-sulfonyl)-phenyl]-propionamide;

3-Cyclopentyl-2-[4-(4-methyl-piperazine-1-sulfonyl)-phenyl]-N-(5-methyl-thiazol-2-yl)-propionamide;

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2-{3-Cyclopentyl-2-[4-(4-methyl-piperazine-1-sulfonyl)-phenyl]-propionylamino}-thiazole-4-carboxylic acid;

2-[3-Cyclopentyl-2-(4-diethylsulfamoyl-phenyl)-propionylamino]-6,7-dihydro-4*H*-thiazolo[5,4-*c*]pyridine-5-carboxylic acid tert-butyl ester;

3-Cyclopentyl-2-(4-diethylsulfamoyl-phenyl)-N-(4,5,6,7-tetrahydro-thiazolo[5,4-*c*]pyridin-2-yl)-propionamide;

3-Cyclopentyl-2-(4-diethylsulfamoyl-phenyl)-N-(5-methyl-4,5,6,7-tetrahydro-thiazolo[5,4-*c*]pyridin-2-yl)-propionamide;

3-Cyclopentyl-2-(4-diethylsulfamoyl-phenyl)-N-pyrazin-2-yl-propionamide;

3-Cyclopentyl-2-(4-diethylsulfamoyl-phenyl)-N-pyridin-2-yl-propionamide;

3-Cyclopentyl-2-(4-diethylsulfamoyl-phenyl)-N-(6-trifluoromethyl-pyridin-2-yl)-propionamide;

3-Cyclopentyl-2-(4-diethylsulfamoyl-phenyl)-N-pyrimidin-2-yl-propionamide;

3-Cyclopentyl-2-(4-diethylsulfamoyl-phenyl)-N-thiazol-2-yl-propionamide; and

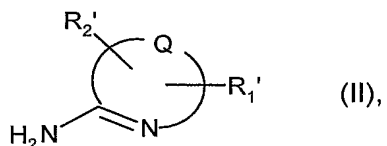
6-[3-Cyclopentyl-2-(4-diethylsulfamoyl-phenyl)-propionylamino]-nicotinic acid;

or an enantiomer thereof; or an enantiomeric mixture thereof; or a pharmaceutically acceptable salt thereof.

Compounds of formula (I) may be prepared using methods well known in the art, e.g., according to Method A or Method B as outlined herein below.

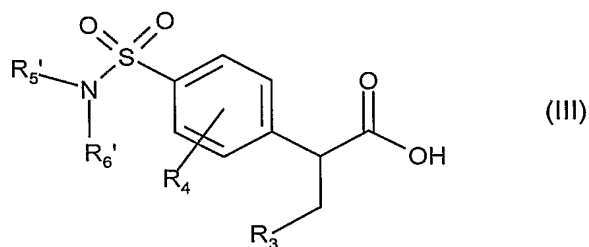
#### Method A:

Compounds of formula (I) may be obtained by coupling an amine of the formula

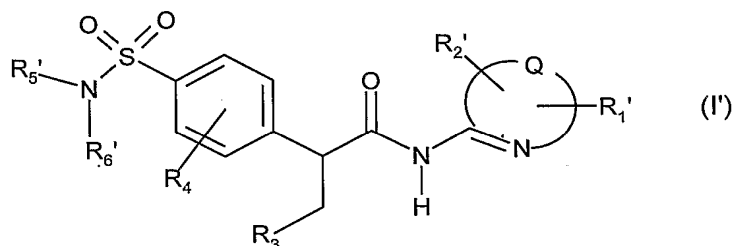


or acid addition salts thereof, wherein  $R_1'$  and  $R_2'$  represents  $R_1$  and  $R_2$ , respectively, as defined herein above, or  $R_1'$  and  $R_2'$  are groups convertible to  $R_1$  and  $R_2$ , respectively, with an activated derivative of a carboxylic acid of the formula

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wherein  $R_3$  and  $R_4$  have meanings as defined herein, and  $R_5'$  and  $R_6'$  represents  $R_5$  and  $R_6$ , respectively, as defined herein above, or  $R_5'$  and  $R_6'$  are groups convertible to  $R_5$  and  $R_6$ , respectively, to afford a compound of the formula



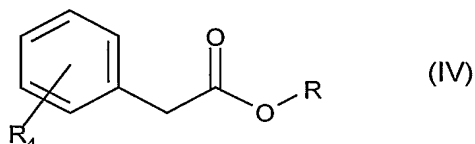
wherein  $R_1'$ ,  $R_2'$ ,  $R_3$ ,  $R_4$ ,  $R_5'$  and  $R_6'$  have meanings as defined for formulae (II) and (III).

In the coupling reaction cited herein above, an activated derivative of a carboxylic acid, e.g., those corresponding to carboxylic acids of formula (III), include acid chlorides, bromides and fluorides, mixed anhydrides, lower alkyl esters and activated esters thereof, and adducts formed with coupling agents, such as 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDCI), 1-hydroxy benzotriazole (HOBt), O-(1,2-dihydro-2-oxo-1-pyridyl)-N,N,N',N'-tetramethyluronium tetrafluoroborate, benzotriazole-1-yl-oxy-tris-pyrrolidino-phosphonium hexafluorophosphate (PyBOP) and the like. Mixed anhydrides are preferably such from pivalic acid, or lower alkyl hemiesters of carbonic acids, such as ethyl or isobutyl analogs. Activated esters include, for example, succinimido, phthalimido or 4-nitrophenyl esters. The reaction of an activated derivative of a carboxylic acid, e.g., those corresponding to carboxylic acids of formula (III), with an amine, e.g., those of formula (II), may be carried out in the presence of a base, such as pyridine, triethylamine (TEA), diisopropylethylamine (DIEA) or N-methylmorpholine (NMM) in an inert organic solvent, such as dichloromethane (DCM), N,N-dimethylformamide (DMF) or tetrahydrofuran (THF), or a mixture of solvents thereof. Carboxylic acids of formula (III) may be converted to their activated derivatives using methods described herein or according to methods generally known in the art, e.g., a carboxylic acid of formula (III) may be treated with a chlorinating agent, such as thionyl chloride or oxalyl chloride, to afford a corresponding acid chloride

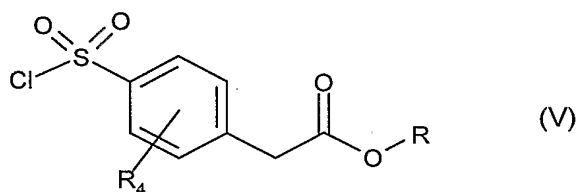
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thereof, or by the treatment of a coupling agent such as EDCI or HOBt, or a mixture of coupling agents thereof.

Amines of formula (II) and carboxylic acids of formula (III) are known, or if they are novel they may be prepared using methods well known in the art or as described herein in the illustrative Examples, or modifications thereof. For example, compounds of formula (III) may be prepared by treating an ester of the formula

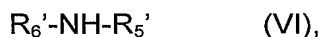


wherein  $R_4$  has a meaning as defined herein above, and R is lower alkyl, preferably, methyl or ethyl, with chlorosulfonic acid to afford a compound of the formula

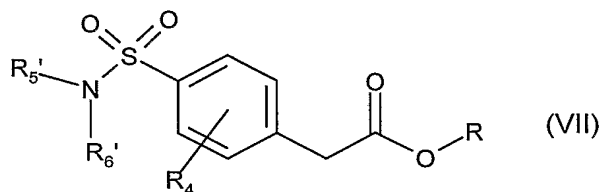


wherein  $R_4$  and R have meanings as defined herein above, optionally in the presence of an intrinsic organic solvent. Preferably, the reaction is carried out without an intrinsic organic solvent.

A compound of formula (V) may then be treated with an amine of the formula



or an acid addition salt thereof, wherein  $R_5'$  and  $R_6'$  have meanings as defined herein above, in the presence of a base, such as pyridine, TEA, DIEA or NMM, in an inert organic solvent, such as DCM, DMF or THF, or a mixture of solvents thereof, to afford a compound of the formula



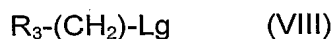
wherein  $R_4$ ,  $R_5'$ ,  $R_6'$  and R have meanings as defined herein above. Preferably, the reaction is conducted at a temperature ranging from about  $-4^{\circ}\text{C}$  to room temperature (RT), more preferably, the reaction temperature is about  $0^{\circ}\text{C}$ . Amines of formula (VI) are known, or if



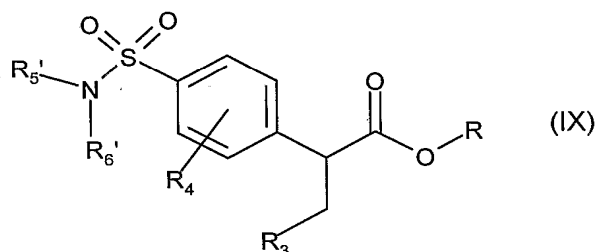
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they are novel they may be prepared using methods well known in the art or as described herein in the illustrative Examples.

A resulting compound of formula (VII) may then be treated with a base, such as sodium hydride, lithium diisopropylamide (LDA) or lithium bis(trimethylsilyl)amide (LHMDS), preferably LDA, followed by addition of an alkylating agent of the formula



wherein  $R_3$  has a meaning as defined herein above, and Lg represents a leaving group, such as chloride, bromide, iodide, mesylate, tosylate or triflate, preferably iodide or triflate, to afford a compound of the formula



wherein  $R_3$ ,  $R_4$ ,  $R_5'$ ,  $R_6'$  and R have meanings as defined herein above. The alkylation step is preferably conducted in a polar organic solvent, such as THF, DMF, N-methylpyrrolidone (NMP), 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyridone (DMPU) or 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (DMTP), or in a mixture of solvents thereof.

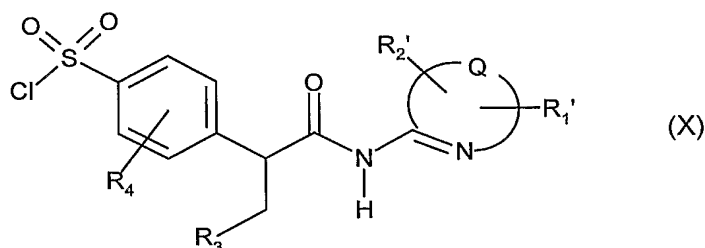
A resulting compound of formula (IX) may then be hydrolyzed, e.g., in the presence of an aqueous base such as sodium, lithium or potassium hydroxide and an organic solvent such as THF or lower alcohol, preferably, methanol or ethanol, to afford a carboxylic acid of formula (III) wherein  $R_3$ ,  $R_4$ ,  $R_5'$  and  $R_6'$  have meanings as defined herein above.

A carboxylic acid of formula (III) may then be coupled with an amine of formula (II), or an acid addition salt thereof, under reaction conditions as described herein above to afford a compound of formula (I') wherein  $R_1'$ ,  $R_2'$ ,  $R_3$ ,  $R_4$ ,  $R_5'$  and  $R_6'$  have meanings as defined herein above, e.g., via conversion of the acid to the corresponding acid chloride or in the presence of a coupling agent such as EDCI, HOBt or PyBOP, or a mixture of coupling agents thereof.

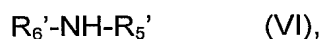
Alternatively, compounds of formula (I) may be prepared as outlined herein below.

Method B:

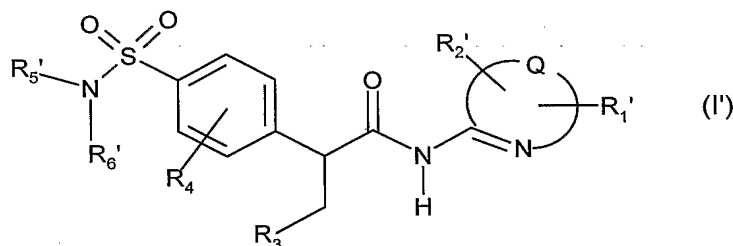
Compounds of formula (I) may be obtained by reacting a compound of the formula



wherein  $R_3$  and  $R_4$  have meanings as defined herein above, and  $R_1'$  and  $R_2'$  represents  $R_1$  and  $R_2$ , respectively, as defined herein above, or  $R_1'$  and  $R_2'$  are a groups convertible to  $R_1$  and  $R_2$ , respectively, with an amine of the formula

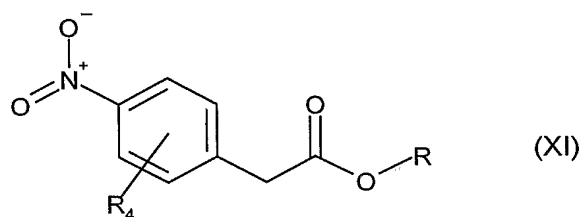


or an acid addition salt thereof, wherein  $R_5'$  and  $R_6'$  have meanings as defined herein above, in the presence of a base, such as pyridine, TEA, DIEA or NMM, in an inert organic solvent, such as DCM, DMF or THF, or a mixture of solvents thereof, to afford a compound of the formula

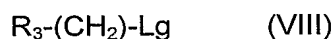


wherein  $R_1'$ ,  $R_2'$ ,  $R_3$ ,  $R_4$ ,  $R_5'$  and  $R_6'$  have meanings as defined herein above.

Compounds of formula (X) may be prepared, e.g., by treating a compound of the formula

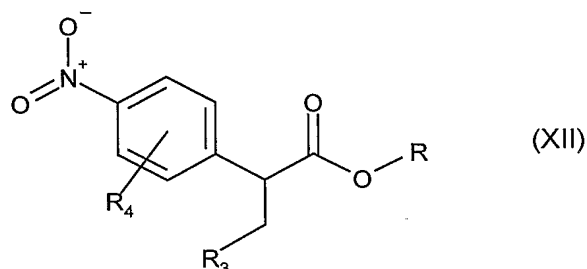


wherein  $R_4$  and  $R$  have meanings as defined herein above, with a base, such as sodium hydride, LDA or LHMDs, preferably LDA, followed by addition of an alkylating agent of the formula



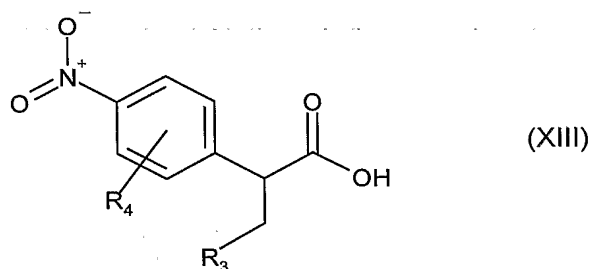
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wherein  $R_3$  has a meaning as defined herein above, and Lg represents a leaving group, such as chloride, bromide, iodide, mesylate, tosylate or triflate, preferably iodide or triflate, to afford a compound of the formula



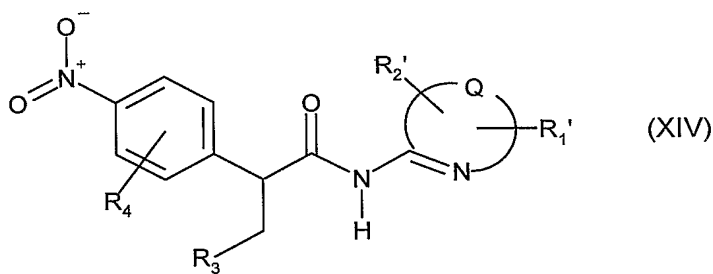
wherein  $R_3$ ,  $R_4$  and R have meanings as defined herein above. The alkylation step is preferably conducted in a polar organic solvent, such as THF, DMF, NMP, DMPU or DMTP, or in a mixture of solvents thereof.

A resulting compound of formula (XII) may then be hydrolyzed, e.g., in the presence of an aqueous base, such as sodium, lithium or potassium hydroxide and an organic solvent such as THF or lower alcohol, preferably, methanol or ethanol, to afford a carboxylic acid of the formula



wherein  $R_3$  and  $R_4$  have meanings as defined herein above.

A carboxylic acid of formula (XIII) may then be coupled with an amine of formula (II) under reaction conditions as described herein above to afford a compound of the formula



wherein  $R_1'$ ,  $R_2'$ ,  $R_3$  and  $R_4$  have meanings as defined herein above, e.g., via conversion of the carboxylic acid to the corresponding acid chloride, or in the presence of a coupling agent, such as EDCI, HOBt or PyBOP, or a mixture of coupling agents thereof.

A resulting compound of formula (XIV) may then be converted to a sulfonyl chloride derivative of formula (X) wherein  $R_1'$ ,  $R_2'$ ,  $R_3$  and  $R_4$  have meanings as defined herein above, by reduction of the nitro group to the amino group, e.g., using iron powder in the presence of a mixture of acetic acid and a lower alcohol, such as ethanol, followed by diazotization reaction and subsequent treatment with, e.g., sulfur dioxide in the presence of copper(II) chloride and acetic acid.

A resulting sulfonyl chloride derivative of formula (X) may then be treated with an amine of formula (VI), or an acid addition salt thereof, wherein  $R_5'$  and  $R_6'$  have meanings as defined herein above, under reaction conditions described herein above to afford a compound of formula (I') wherein  $R_1'$ ,  $R_2'$ ,  $R_3$ ,  $R_4$ ,  $R_5'$  and  $R_6'$  have meanings as defined herein above.

The processes described herein above may be conducted under inert atmosphere, preferably under nitrogen atmosphere.

In starting compounds and intermediates which are converted to the compounds of the present invention in a manner described herein, functional groups present, such as amino, thiol, carboxyl and hydroxyl groups, are optionally protected by conventional protecting groups that are common in preparative organic chemistry. Protected amino, thiol, carboxyl and hydroxyl groups are those that can be converted under mild conditions into free amino thiol, carboxyl and hydroxyl groups without the molecular framework being destroyed or other undesired side reactions taking place.

The purpose of introducing protecting groups is to protect the functional groups from undesired reactions with reaction components under the conditions used for carrying out a desired chemical transformation. The need and choice of protecting groups for a particular reaction is known to those skilled in the art and depends on the nature of the functional group to be protected (hydroxyl group, amino group, etc.), the structure and stability of the molecule of which the substituent is a part and the reaction conditions.

Well-known protecting groups that meet these conditions and their introduction and removal are described, e.g., in McOmie, "Protective Groups in Organic Chemistry", Plenum Press,

London, NY (1973); and Greene and Wuts, "Protective Groups in Organic Synthesis", John Wiley and Sons, Inc., NY (1999).

The above-mentioned reactions are carried out according to standard methods, in the presence or absence of diluent, preferably, such as are inert to the reagents and are solvents thereof, of catalysts, condensing or said other agents, respectively and/or inert atmospheres, at low temperatures, RT or elevated temperatures, preferably at or near the boiling point of the solvents used, and at atmospheric or super-atmospheric pressure. The preferred solvents, catalysts and reaction conditions are set forth in the appended illustrative Examples.

The invention further includes any variant of the present processes, in which an intermediate product obtainable at any stage thereof is used as starting material and the remaining steps are carried out, or in which the starting materials are formed *in situ* under the reaction conditions, or in which the reaction components are used in the form of their salts or optically pure antipodes.

Compounds of the invention and intermediates can also be converted into each other according to methods generally known *per se*.

The invention also relates to any novel starting materials, intermediates and processes for their manufacture.

Depending on the choice of starting materials and methods, the new compounds may be in the form of one of the possible isomers or mixtures thereof, for example, as substantially pure geometric (*cis* or *trans*) isomers, diastereomers, optical isomers (enantiomers, antipodes), racemates or mixtures thereof. The aforesaid possible isomers or mixtures thereof are within the purview of this invention.

Any resulting mixtures of isomers can be separated on the basis of the physicochemical differences of the constituents, into the pure geometric or optical isomers, diastereomers, racemates, for example, by chromatography and/or fractional crystallization.

Any resulting racemates of final products or intermediate, e.g., acids of formulae (III) and (XIII), can be resolved into the optically pure isomers by known methods, e.g., by separation of the diastereomeric salts thereof, obtainable with an optically active acid or base and liberating the optically active acidic or basic compound, respectively, e.g., acids of formulae

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(III) and (XIII) can be resolved using optically active 1-phenylethylamine. Similarly, the compounds of the instant invention having a basic moiety may be resolved into their optical isomers, e.g., by fractional crystallization of a salt formed with an optically active acid, e.g., tartaric acid, dibenzoyl tartaric acid, diacetyl tartaric acid, di-O,O'-*p*-toluoyl tartaric acid, mandelic acid, malic acid or camphor-10-sulfonic acid. Racemic products can also be resolved by chiral chromatography, e.g., high pressure liquid chromatography (HPLC) using a chiral adsorbent. Alternatively, optically pure isomers of compounds of the present invention may be obtained by employing chiral reagents. For example, an optical isomer, preferably the R isomer, of a compound of the present invention may be prepared employing chiral auxiliaries such as the Evans auxiliary.

Finally, compounds of the invention are either obtained in the free form, or in a salt form thereof, preferably, in a pharmaceutically acceptable salt form thereof, or as a prodrug derivative thereof.

Compounds of the instant invention which contain acidic groups may be converted into salts with pharmaceutically acceptable bases. Such salts include alkali metal salts, like sodium, lithium and potassium salts; alkaline earth metal salts, like calcium and magnesium salts; ammonium salts with organic bases, e.g., trimethylamine salts, diethylamine salts, tris(hydroxymethyl)methylamine salts, dicyclohexylamine salts and N-methyl-D-glucamine salts; salts with amino acids like arginine, lysine and the like. Salts may be formed using conventional methods, advantageously in the presence of an ethereal or alcoholic solvent, such as a lower alkanol. From the solutions of the latter, the salts may be precipitated with ethers, e.g., diethyl ether. Resulting salts may be converted into the free compounds by treatment with acids. These or other salts can also be used for purification of the compounds obtained.

Compounds of the invention, in general, may be converted into acid addition salts, especially pharmaceutically acceptable salts. These are formed, e.g., with inorganic acids, such as mineral acids, e.g., sulfuric acid, phosphoric or hydrohalic acid, or with organic carboxylic acids, such as (C<sub>1-4</sub>)alkanecarboxylic acids which, e.g., are unsubstituted or substituted by halogen, e.g., acetic acid, such as saturated or unsaturated dicarboxylic acids, e.g., oxalic, succinic, maleic or fumaric acid, such as hydroxycarboxylic acids, e.g., glycolic, lactic, malic, tartaric or citric acid, such as amino acids, e.g., aspartic or glutamic acid, or with organic sulfonic acids, such as (C<sub>1-4</sub>)alkylsulfonic acids, e.g., methanesulfonic acid; or arylsulfonic

acids which are unsubstituted or substituted (for example by halogen). Preferred are salts formed with hydrochloric acid, maleic acid and methanesulfonic acid.

Prodrug derivatives of any compound of the invention are derivatives of said compounds which following administration release the parent compound *in vivo* via some chemical or physiological process, e.g., a prodrug on being brought to the physiological pH or through enzyme action is converted to the parent compound. Exemplary prodrug derivatives are, e.g., esters of free carboxylic acids and S-acyl and O-acyl derivatives of thiols, alcohols or phenols, wherein acyl has a meaning as defined herein. Preferred are pharmaceutically acceptable ester derivatives convertible by solvolysis under physiological conditions to the parent carboxylic acid. Such ester derivatives include, but are not limited to, lower alkyl esters, cycloalkyl esters, lower alkenyl esters, benzyl esters, mono- or di-substituted lower alkyl esters, such as the  $\omega$ -(amino, mono- or di-lower alkylamino, carboxy, lower alkoxy carbonyl)-lower alkyl esters, the  $\alpha$ -(lower alkanoyloxy, lower alkoxy carbonyl or di-lower alkylaminocarbonyl)-lower alkyl esters, such as the pivaloyloxymethyl ester and others conventionally used in the art.

In view of the close relationship between the free compounds, the prodrug derivatives and the compounds in the form of their salts, whenever a compound is referred to in this context, a prodrug derivative and a corresponding salt is also intended, provided such is possible or appropriate under the circumstances.

The compounds, including their salts, can also be obtained in the form of their hydrates, or include other solvents used for their crystallization.

As described herein above, the compounds of the present invention may be employed for the treatment of conditions mediated by glucokinase activity. Such compounds may thus be employed therapeutically for the treatment of impaired glucose tolerance, type 2 diabetes and obesity.

The present invention further provides pharmaceutical compositions comprising a therapeutically effective amount of a pharmacologically active compound of the instant invention, alone or in combination with one or more pharmaceutically acceptable carriers.

The pharmaceutical compositions according to the invention are those suitable for enteral, such as oral or rectal; transdermal and parenteral administration to mammals, including

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man, for the treatment of conditions mediated by glucokinase activity. Such conditions include impaired glucose tolerance, type 2 diabetes and obesity.

Thus, the pharmacologically active compounds of the invention may be employed in the manufacture of pharmaceutical compositions comprising an effective amount thereof in conjunction or admixture with excipients or carriers suitable for either enteral or parenteral application. Preferred are tablets and gelatin capsules comprising the active ingredient together with:

- a) diluents, e.g., lactose, dextrose, sucrose, mannitol, sorbitol, cellulose and/or glycine;
- b) lubricants, e.g., silica, talcum, stearic acid, its magnesium or calcium salt and/or polyethyleneglycol; for tablets also
- c) binders, e.g., magnesium aluminum silicate, starch paste, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose and or polyvinylpyrrolidone; if desired
- d) disintegrants, e.g., starches, agar, alginic acid or its sodium salt, or effervescent mixtures; and/or
- e) absorbants, colorants, flavors and sweeteners.

Injectable compositions are preferably aqueous isotonic solutions or suspensions, and suppositories are advantageously prepared from fatty emulsions or suspensions.

Said compositions may be sterilized and/or contain adjuvants, such as preserving, stabilizing, wetting or emulsifying agents, solution promoters, salts for regulating the osmotic pressure and/or buffers. In addition, they may also contain other therapeutically valuable substances. Said compositions are prepared according to conventional mixing, granulating or coating methods, respectively, and contain about 0.1-75%, preferably about 1-50%, of the active ingredient.

Suitable formulations for transdermal application include a therapeutically effective amount of a compound of the invention with carrier. Advantageous carriers include absorbable pharmacologically acceptable solvents to assist passage through the skin of the host. Characteristically, transdermal devices are in the form of a bandage comprising a backing member, a reservoir containing the compound optionally with carriers, optionally a rate controlling barrier to deliver the compound of the skin of the host at a controlled and predetermined rate over a prolonged period of time, and means to secure the device to the skin.



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Accordingly, the present invention provides pharmaceutical compositions as described above for the treatment of conditions mediated by glucokinase activity, preferably, impaired glucose tolerance, type 2 diabetes and obesity.

The pharmaceutical compositions may contain a therapeutically effective amount of a compound of the invention as defined above, either alone or in a combination with another therapeutic agent, e.g., each at an effective therapeutic dose as reported in the art. Such therapeutic agents include:

- a) anti-diabetic agents, such as insulin, insulin derivatives and mimetics; insulin secretagogues such as the sulfonylureas, e.g., Glipizide, glyburide and Amaryl; insulinotropic sulfonylurea receptor ligands such as meglitinides, e.g., nateglinide and repaglinide; thiazolidone derivatives such as glitazones, e.g., pioglitazone and rosiglitazone; protein tyrosine phosphatase-1B (PTP-1B) inhibitors such as PTP-112; GSK3 (glycogen synthase kinase-3) inhibitors such as SB-517955, SB-4195052, SB-216763, NN-57-05441 and NN-57-05445; RXR ligands such as GW-0791 and AGN-194204; sodium-dependent glucose co-transporter inhibitors such as T-1095; glycogen phosphorylase A inhibitors such as BAY R3401; biguanides such as metformin; alpha-glucosidase inhibitors such as acarbose; GLP-1 (glucagon like peptide-1), GLP-1 analogs such as Exendin-4 and GLP-1 mimetics; modulators of PPARs (peroxisome proliferator-activated receptors), e.g., non-glitazone type PPAR $\gamma$  agonists such as N-(2-benzoylphenyl)-L-tyrosine analogues, e.g. GI-262570, and JTT501; DPPIV (dipeptidyl peptidase IV) inhibitors such as LAF237, MK-0431, saxagliptin and GSK23A; SCD-1 (stearoyl-CoA desaturase-1) inhibitors; DGAT1 and DGAT2 (diacylglycerol acyltransferase 1 and 2) inhibitors; ACC2 (acetyl CoA carboxylase 2) inhibitors; and breakers of AGE (advanced glycation end products);
- b) anti-dyslipidemic agents such as 3-hydroxy-3-methyl-glutaryl coenzyme A (HMG-CoA) reductase inhibitors, e.g., lovastatin, pitavastatin, simvastatin, pravastatin, cerivastatin, mevastatin, velostatin, fluvastatin, dalvastatin, atorvastatin, rosuvastatin and rivastatin; HDL increasing compounds such as cholesterol ester transfer protein (CETP) inhibitors, e.g., JTT705; Apo-A1 analogs and mimetics; squalene synthase inhibitors; FXR (farnesoid X receptor) and LXR (liver X receptor) ligands; cholestyramine; fibrates; nicotinic acid; and aspirin;
- c) anti-obesity agents such as phentermine, leptin, bromocriptine, dexamphetamine, amphetamine, fenfluramine, dexfenfluramine, sibutramine, orlistat, dexfenfluramine, mazindol, phentermine, phendimetrazine, diethylpropion, fluoxetine, bupropion, topiramate,

diethylpropion, benzphetamine, phenylpropanolamine, ecopipam, ephedrine, and pseudoephedrine; cholesterol absorption modulators such as ZETIA® and KT6-971; and cannabinoid receptor antagonists such as rimonabant; and

d) anti-hypertensive agents, e.g., loop diuretics such as ethacrynic acid, furosemide and torsemide; angiotensin converting enzyme (ACE) inhibitors such as benazepril, captopril, enalapril, fosinopril, lisinopril, moexipril, perinodopril, quinapril, ramipril and trandolapril; inhibitors of the Na-K-ATPase membrane pump such as digoxin; neutralendopeptidase (NEP) inhibitors; ACE/NEP inhibitors such as omapatrilat, sampatrilat and fasidotril; angiotensin II antagonists such as candesartan, eprosartan, irbesartan, losartan, telmisartan and valsartan, in particular valsartan; renin inhibitors such as ditekiren, zankiren, terlakiren, aliskiren, RO 66-1132 and RO-66-1168;  $\beta$ -adrenergic receptor blockers such as acebutolol, atenolol, betaxolol, bisoprolol, metoprolol, nadolol, propranolol, sotalol and timolol; inotropic agents such as digoxin, dobutamine and milrinone; calcium channel blockers such as amlodipine, bepridil, diltiazem, felodipine, nicardipine, nimodipine, nifedipine, nisoldipine and verapamil; aldosterone receptor antagonists such as eplerenone; and aldosterone synthase inhibitors such as anastrozole and fadrazole.

Other specific anti-diabetic compounds are described by Patel Mona in *Expert Opin Investig Drugs*, 2003, 12(4), 623-633, in the figures 1 to 7, which are herein incorporated by reference. A compound of the present invention may be administered either simultaneously, before or after the other active ingredient, either separately by the same or different route of administration or together in the same pharmaceutical formulation.

The structure of the therapeutic agents identified by code numbers, generic or trade names may be taken from the actual edition of the standard compendium "The Merck Index" or from databases, e.g., Patents International (e.g. IMS World Publications). The corresponding content thereof is hereby incorporated by reference.

Accordingly, the present invention provides pharmaceutical compositions comprising a therapeutically effective amount of a compound of the invention in combination with a therapeutically effective amount of another therapeutic agent, preferably selected from anti-diabetics, hypolipidemic agents, anti-obesity agents or anti-hypertensive agents, most preferably from antidiabetics or hypolipidemic agents as described above.

The present invention further relates to pharmaceutical compositions as described above for use as a medicament.

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The present invention further relates to use of pharmaceutical compositions or combinations as described above for the preparation of a medicament for the treatment of conditions mediated by glucokinase activity, preferably, impaired glucose tolerance, type 2 diabetes and obesity.

Thus, the present invention also relates to a compound of formula (I) for use as a medicament; to the use of a compound of formula (I) for the preparation of a pharmaceutical composition for the prevention and/or treatment of conditions mediated by glucokinase activity, and to a pharmaceutical composition for use in conditions mediated by glucokinase activity comprising a compound of formula (I), or a pharmaceutically acceptable salt thereof, in association with a pharmaceutically acceptable diluent or carrier therefore.

The present invention further provides a method for the prevention and/or treatment of conditions mediated by glucokinase activity, which comprises administering a therapeutically effective amount of a compound of the present invention.

A unit dosage for a mammal of about 50-70 kg may contain between about 1 mg and 1000 mg, advantageously between about 5-500 mg of the active ingredient. The therapeutically effective dosage of active compound is dependent on the species of warm-blooded animal (mammal), the body weight, age and individual condition, on the form of administration, and on the compound involved.

In accordance with the foregoing the present invention also provides a therapeutic combination, e.g., a kit, kit of parts, e.g., for use in any method as defined herein, comprising a compound of formula (I), or a pharmaceutically acceptable salt thereof, to be used concomitantly or in sequence with at least one pharmaceutical composition comprising at least another therapeutic agent, preferably selected from anti-diabetic agents, hypolipidemic agents, anti-obesity agents and anti-hypertensive agents, or a pharmaceutically acceptable salt thereof. The kit may comprise instructions for its administration.

Similarly, the present invention provides a kit of parts comprising: (i) a pharmaceutical composition of the invention; and (ii) a pharmaceutical composition comprising a compound selected from an anti-diabetic, a hypolipidemic agent, an anti-obesity agent and an anti-hypertensive agent, or a pharmaceutically acceptable salt thereof, in the form of two separate units of the components (i) to (ii).

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Likewise, the present invention provides a method as defined above comprising co-administration, e.g., concomitantly or in sequence, of a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof, and a second drug substance, said second drug substance being an anti-diabetic, a hypolipidemic agent, an anti-obesity agent or an anti-hypertensive agent, e.g., as indicated above.

Preferably, a compound of the invention is administered to a mammal in need thereof.

Preferably, a compound of the invention is used for the treatment of a disease which responds to modulation of the glucokinase activity.

Preferably, the condition associated with glucokinase activity is selected from impaired glucose tolerance, type 2 diabetes and obesity.

Finally, the present invention provides a method or use which comprises administering a compound of formula (I) in combination with a therapeutically effective amount of an anti-diabetic agent, a hypolipidemic agent, an anti-obesity agent or an anti-hypertensive agent.

Ultimately, the present invention provides a method or use which comprises administering a compound of formula (I) in the form of a pharmaceutical composition as described herein.

As used throughout the specification and in the claims, the term "treatment" embraces all the different forms or modes of treatment as known to those of the pertinent art and in particular includes preventive, curative, delay of progression and palliative treatment.

The above-cited properties are demonstrable *in vitro* and *in vivo* tests using advantageously mammals, e.g., mice, rats, dogs, monkeys or isolated organs, tissues and preparations thereof. Said compounds can be applied *in vitro* in the form of solutions, e.g., preferably aqueous solutions, and *in vivo* either enterally, parenterally, advantageously intravenously, e.g., as a suspension or in aqueous solution. The dosage *in vitro* may range between about  $10^{-2}$  molar and  $10^{-9}$  molar concentrations. A therapeutically effective amount *in vivo* may range depending on the route of administration, between about 0.1 mg/kg and 1000 mg/kg, preferably between about 1 mg/kg and 100 mg/kg.

The activity of compounds according to the invention may be assessed by the following methods or methods well-described in the art:

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For example, the glucokinase activation *in vitro* may be determined by measuring the activation of recombinant GST-GK by a compound of the present invention in the absence or the presence of GKRP, a 68,000 Da protein inhibitor of GK. In these assays, formation of glucose-6-phosphate is coupled directly to the formation of thio-NADH. GST-GK catalyzes the reaction of glucose and Mg-ATP to produce glucose-6-phosphate and ADP. Glucose-6-phosphate dehydrogenase (G6PDH) reduces thionicotinamide (thio-NAD) to thio-NADH. The assay measures the formation of thio-NADH at 405 nM.

The basic GK assay components are as follows: 25 mM HEPES (pH 7.1), 25 mM KCl, 2.5 mM MgCl<sub>2</sub>, 1 mM ATP (Sigma A-5394), 1 mM DTT, 1 mM thio-NAD (Sigma T-7375), 80 units/mL G6PDH (Sigma G-5885), 10 mM glucose and 110 nM GST-GK. For assessing reversal of GK inhibition by GKRP, 20  $\mu$ M Fructose-6-phosphate (F-6-P) and 370 nM recombinant GKRP are added to these assay components. Fructose-1-phosphate (F-1-P) at 1  $\mu$ M is used as a control in the GK/GKRP assay. F-1-P reverses inhibition of GST-GK by GKRP.

The assay is done in standard, 96-well, round-bottom plates (Corning) and the total assay volume is 25  $\mu$ L. Test compounds are serially diluted into 100% DMSO and 0.5  $\mu$ L of diluted compound in 100% DMSO is added to the assay plate. Assay reagents (24.5  $\mu$ L) are added using a Zymark robotic platform. Buffer, containing HEPES, MgCl<sub>2</sub>, KCl, thio-NAD, G6PDH, glucose and GST-GK, are added (5  $\mu$ L) using the Zymark 8-channel hand pipet. For the GK/GKRP assay, GKRP and F-6-P are also included. The reaction is then initiated by adding 19.5  $\mu$ L of buffer containing HEPES, MgCl<sub>2</sub>, KCl, DTT and ATP using the Zymark Reagent Addition Station/Reagent Addition Module. The plates are read kinetically over 10 min at 25°C using a SpectraMax Plus microplate spectrophotometer (Molecular Devices, Sunnyvale, CA) to monitor the increase in optical density at 405 nm. The GK activity in wells containing test compounds is compared with activity in DMSO control wells. The concentration of compound that produces a 50% increase in the activity of GK is calculated and expressed as EC<sub>50</sub>. All of the compounds described in the Examples had an EC<sub>50</sub> value less than or equal to 200  $\mu$ M and preferably less than 20  $\mu$ M. Most preferable are compounds with EC<sub>50</sub> less than 2  $\mu$ M which exhibited at least a 2-fold increase in % GK activation versus control.

The glucokinase activation in rat hepatocytes may be determined as follows:

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Hepatocytes are isolated by collagenase perfusion of the livers of overnight-fasted male Harlan Sprague-Dawley rats (Charles River Laboratories, Raleigh, NC) as previously described (see Berry et al., *J. Cell Biol.*, Vol. 43, pp. 506-520 (1969)). The cells are washed three times each with 100 mL of glucose-free Dulbecco's Modified Eagle medium (DMEM, Gibco BRL) containing 5% fetal bovine serum (FBS) and then suspended in glucose-free DMEM/5% FBS. Cells are plated in collagen coated 24-well plates (Becton Dickinson) at a density of  $3 \times 10^5$  cells/well in 1 mL of William's Medium E (Sigma) supplemented with 5% FBS, and incubated at 37°C in 5% CO<sub>2</sub>/95% air. After cell attachment (~4 h), the medium is replaced with serum-free DMEM containing 5 mM glucose and 10 nM dexamethasone (Sigma), and cells are cultured further for 16-20 h prior to use.

The rate of glucose phosphorylation is determined by the release of <sup>3</sup>H<sub>2</sub>O from [2-<sup>3</sup>H]glucose. The medium from the cultured hepatocytes is removed, and the cells are pre-incubated in 150 µL of fresh serum-free DMEM containing 5 mM glucose and compound (1, 10 and 30 µM) or DMSO for 3 h at 37°C. The final concentration of DMSO is 0.2%. The medium is then removed and 150 µL of a fresh mixture of DMEM/5 mM glucose containing compound or DMSO, and 1 µCi of [2-<sup>3</sup>H]glucose (NEN) is added. As a positive control for stimulation of glucose phosphorylation, cells are pre-incubated in serum-free DMEM/5 mM glucose medium containing DMSO for 3 h and then are incubated for 1 h in labeled glucose medium containing 0.5 mM fructose/DMSO (precursor of F-1-P, AnalaR<sup>®</sup> from BDH). All conditions are tested in quadruplicate where one well per plate received 200 µL of the appropriate medium plus labeled glucose (instead of 150 µL) of which 50 µL is immediately removed and placed in a 1.2 mL microfuge tube (Costar) containing 10 µL of 1 N HCl. This sample is used as a 0-minute time point for determining background <sup>3</sup>H<sub>2</sub>O release (exchange values). Following the addition of the labeled glucose media, hepatocytes are incubated at 37°C on a slow moving rocker for 1 h.

On termination of the incubation, 50 µL of the culture medium is collected into microfuge tubes containing 10 µL of 1 N HCl, and determination of <sup>3</sup>H<sub>2</sub>O. The tubes are left uncapped and each is placed inside a 20 mL glass scintillation vial (Wheaton) containing 1.5 mL of deionized water. The vials are capped tightly and incubated at 37°C in a dry incubator for 2 days (<sup>3</sup>H<sub>2</sub>O from the reaction mixture will equilibrate with the water in the vial). A standard curve is generated using [<sup>3</sup>H]H<sub>2</sub>O (NEN) to correct for exchange. 50 µL aliquots of serial dilutions of the labeled water are added to 10 µL of 1 N HCl and exchange is performed as described for the samples (typically, approximately 90% exchange is observed). The

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microfuge tubes are then removed from the vials carefully to minimize the removal of any water from the vial and 18 mL of scintillation cocktail (Ready Safe, Beckman Coulter) is then added to each vial. The  $^3\text{H}$ -label recovered from  $[2\text{-}^3\text{H}]\text{glucose}$  in the water is determined using a Beckman Model LS500 scintillation counter and the counts (minus the 0-time point) are corrected for recovery of  $^3\text{H}_2\text{O}$ . The amount of glucose de-tritiated in nanomoles/h per  $10^6$  cells is calculated, and the results are expressed as percent increase over the DMSO control.

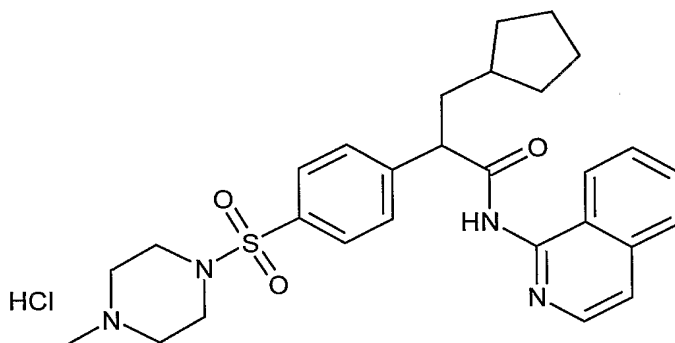
The glucokinase activation *in vivo* may be determined as follows:

Male C57BL mice (Jackson Lab, Bar Harbor, ME) are housed 2 per cage in a reversed light cycle room (light on from 8:00 p.m. to 8:00 a.m.) and given access to food and water *ad libitum*. To induce DIO, the mice are given a high fat diet (D12492 with 60% caloric intake from fat, Research Diets, New Brunswick, NJ) from 4 weeks of age and maintained on the diet before being used. The DIO mice are used at 25 weeks of age. On the day of the study, animals are fasted at 7:30 a.m. Body weight measurement and basal blood sample collection are conducted at 10:00 a.m. Plasma glucose values are then determined. Animals are assigned into five groups ( $n=7/\text{group}$ ) with the means of plasma glucose matched among the groups. At 10:30 a.m. animals are dosed with vehicle (water) or compound in vehicle with a dose volume of 5 ml/kg. The test compound is given at 3, 10, 30, or 100 mg/kg. One hour after vehicle or compound dosing, a blood sample (at 0 min) is taken followed by an oral glucose tolerance test (OGTT) at 1 g/kg (20% glucose in water) and a dose volume of 5 ml/kg. Blood samples are collected at 30, 60 and 120 min following the glucose administration. The animals are refed after the OGTT. Blood samples are taken via tail bleeding. Plasma glucose concentrations are determined using a glucose meter (Ascensia Elite, Bayer Corp., Mishawaka, IN). Blood samples are collected in tubes (Microvette CB300, Aktiengesellschaft & Co., Numbrecht, Germany) which contain EDTA (ethylenediaminetetraacetic acid) to prevent blood clotting. After blood sample collection, the tubes are kept on ice before being centrifuged. Plasma portion of the blood samples is obtained by centrifugation at  $10,000 \times g$  for 10 min at  $4^\circ\text{C}$  and then stored at  $-80^\circ\text{C}$ . Plasma insulin levels are determined by Luminex assay using Mouse Endocrine Lincoplex kit (Linco Research, Inc., St. Charles, MO). Data are reported as means  $\pm$  SEM. Statistical analysis is performed using a one-way or two-way analysis of variance (ANOVA) followed by a Tukey post-hoc test to compare the difference among the groups. Statistical significance is accepted at the level of  $p<0.05$ .

The following Examples are intended to illustrate the invention and are not to be construed as being limitations thereon. If not mentioned otherwise, all evaporations are performed under reduced pressure, preferably between about 50 mmHg and 100 mmHg. The structure of final products, intermediates and starting materials is confirmed by standard analytical methods, e.g., microanalysis, melting point (m.p.) and spectroscopic characteristics, e.g., MS, IR and NMR. Abbreviations used are those conventional in the art.

### **Example 1**

#### **3-Cyclopentyl-N-isoquinolin-1-yl-2-[4-(4-methyl-piperazine-1-sulfonyl)-phenyl]-propionamide hydrochloride**



##### **A. 1-(4-Bromo-benzenesulfonyl)-4-methyl-piperazine**

N-methylmorpholine (60 g, 65 mL, 0.6 mol) is dissolved in DCM (100 mL), to which 1-methylpiperazine (30.5 g, 0.3 mol) is added. The reaction is cooled to 0°C, after which a solution of 4-bromo-benzenesulfonyl chloride (75.8 g, 0.296 mol) in DCM (100 mL) is added dropwise. The reaction is allowed to warm to RT overnight. The reaction mixture is then concentrated and water (1 L) is added. The solids that are formed are filtered and the filtrate is extracted with EtOAc (500 mL). The organic layer is washed with saturated brine, dried over MgSO<sub>4</sub>, filtered and concentrated to afford 1-(4-bromo-benzenesulfonyl)-4-methyl-piperazine as a pale yellow solid: LC/MS 321.0 (M+1); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 2.3 (s, 3 H) 2.5 (m, 4 H) 3.0 (m, 4 H) 7.6 (dt, J=8.8, 2.0 Hz, 2 H) 7.7 (dt, J=8.8, 2.1 Hz, 2 H).

##### **B. [4-(4-Methyl-piperazine-1-sulfonyl)-phenyl]-acetic acid ethyl ester**

The title A compound, 1-(4-bromo-benzenesulfonyl)-4-methyl-piperazine (5.00 g, 15.663 mmol), ethyl acetoacetate (2.97 mL, 23.495 mmol), 2-(di-tert-butylphosphino)-2-methyl biphenyl (98 mg, 0.313 mmol), palladium acetate (105 mg, 0.157 mmol) and potassium phosphate (9.97 g, 46.989 mmol) are charged to a flask. Toluene (60 mL) is added. The reaction is heated at 90°C overnight, then cooled to RT. The reaction mixture is poured onto



ethyl acetate and water. The organic layer is dried over anhydrous sodium sulfate, filtered and concentrated to afford a brown oil. This is chromatographed using 0→20% methanol in ethyl acetate to afford [4-(4-methyl-piperazine-1-sulfonyl)-phenyl]-acetic acid ethyl ester as a tan solid which contains ~8% of the acylated material: LC/MS 327.1 (M+1); <sup>1</sup>H NMR (400 MHz, DMSO-D<sub>6</sub>) δ 1.2 (t, J=7.1 Hz, 3 H) 2.1 (s, 3 H) 2.3 (m, 4 H) 2.9 (d, J=4.3 Hz, 4 H) 3.8 (s, 2 H) 4.1 (q, J=7.1 Hz, 2 H) 7.5 (d, J=8.3 Hz, 2 H) 7.6 (d, 7.7 (m, 2 H).

**C. 3-Cyclopentyl-2-[4-(4-methyl-piperazine-1-sulfonyl)-phenyl]-propionic acid ethyl ester**

DIEA (0.742 g, 7.32 mmol) is dissolved in THF (10 mL) and cooled to -78°C, under an atmosphere of N<sub>2</sub>. n-BuLi (2.5M in hexanes, 2.25 mL, 5.63 mmol) is added to this slowly. The resulting solution is stirred at -78°C for 15 min. A solution of the title B compound, [4-(4-methyl-piperazine-1-sulfonyl)-phenyl]-acetic acid ethyl ester (1.84 g, 5.63 mmol) in THF/DMPU (10 mL/5 mL) is then added dropwise. The reaction is then stirred at -78°C for one hour. A solution of cyclopentylmethyl iodide (1.18 g, 5.63 mmol) in THF/DMPU (10 mL/5 mL) is then added dropwise and the reaction is allowed to warm to RT overnight. The reaction is then poured into saturated NH<sub>4</sub>Cl solution and extracted with EtOAc. The organic layer is dried over MgSO<sub>4</sub>, filtered and concentrated to afford a brown oil. This is purified by flash chromatography (0→2% EtOAc in MeOH) to afford 3-cyclopentyl-2-[4-(4-methyl-piperazine-1-sulfonyl)-phenyl]-propionic acid ethyl ester as a brown oil: <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.12 (m, 2H) 1.24 (m, 3H) 1.50 (m, 2H) 1.60 (m, 3H) 1.76 (m, 2H) 2.08 (m, 2H) 2.27 (s, 3H) 2.47 (s, 4H) 3.04 (s, 4H) 3.65 (m, 1H) 4.13 (m, 2H) 7.48 (m, 2H) 7.69 (m, 2H); LC/MS 409.3 (M + 1).

**D. 3-Cyclopentyl-2-[4-(4-methyl-piperazine-1-sulfonyl)-phenyl]-propionic acid hydrochloride**

The title C compound, 3-cyclopentyl-2-[4-(4-methyl-piperazine-1-sulfonyl)-phenyl]-propionic acid ethyl ester (1.98 g, 4.846 mmol) is dissolved in THF. To this is added a solution of sodium hydroxide (94 mg, 4.846 mmol) in water. The reaction is stirred at RT overnight, then concentrated to dryness. The resulting solid is dissolved in 4 N hydrochloric acid in dioxane and stirred at RT for 30 min. Concentration affords 3-cyclopentyl-2-[4-(4-methyl-piperazine-1-sulfonyl)-phenyl]-propionic acid hydrochloride salt containing one equivalent of sodium chloride: LC/MS 381.3 (M+1); <sup>1</sup>H NMR (400 MHz, DMSO-D<sub>6</sub>) δ 1.1 (m, 2 H) 1.4 (m, 2 H) 1.5 (m, 3 H) 1.7 (m, 3 H) 2.0 (ddd, J=13.3, 7.7, 7.6 Hz, 1 H) 2.7 (m, 5 H) 3.1 (d, J=10.1

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Hz, 2 H) 3.4 (d,  $J=12.1$  Hz, 2 H) 3.7 (m, 3 H) 7.6 (d,  $J=8.3$  Hz, 2 H) 7.7 (d,  $J=8.3$  Hz, 2 H) 11.3 (s, 1 H).

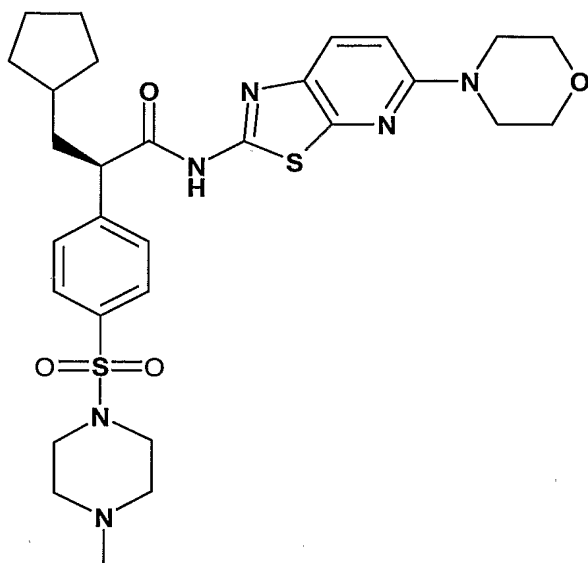
**E. 3-Cyclopentyl-N-isoquinolin-1-yl-2-[4-(4-methyl-piperazine-1-sulfonyl)-phenyl]-propionamide hydrochloride**

The title D compound, 3-cyclopentyl-2-[4-(4-methyl-piperazine-1-sulfonyl)-phenyl]-propionic acid hydrochloride (150 mg, 0.346 mmol) is slurried in DMF (3 mL) with TEA (97  $\mu$ L, 0.692 mmol) and cooled to 0°C. After 45 min, isoquinolin-1-ylamine (50 mg, 0.346 mmol) in pyridine (1 mL) is added dropwise. The reaction is allowed to stir and warm to RT overnight. The reaction is diluted with ethyl acetate and water. The organic layer is separated, dried over anhydrous sodium sulfate, filtered and concentrated to afford a brown oil. Purification via flash chromatography using 0→2% methanol in ethyl acetate affords the pure product. This is dissolved in 1 M hydrochloric acid in ether and stirred at RT for 30 min, then concentrated. Dissolution in water followed by lyophilization affords 3-cyclopentyl-N-isoquinolin-1-yl-2-[4-(4-methyl-piperazine-1-sulfonyl)-phenyl]-propionamide, hydrochloric salt as a yellow solid: LC/MS 507.4 (M+1), 505.5 (M-1);  $^1\text{H}$  NMR (400 MHz, DMSO- $\text{D}_6$ )  $\delta$  1.2 (m, 2 H) 1.5 (m, 2 H) 1.6 (m, 2 H) 1.7 (m, 2 H) 1.8 (dd,  $J=13.3, 6.9$  Hz, 2 H) 2.2 (dd,  $J=13.0, 7.5$  Hz, 1 H) 2.7 (m, 5 H) 2.9 (s, 1 H) 3.1 (s, 1 H) 3.4 (d,  $J=11.9$  Hz, 2 H) 3.8 (d,  $J=12.4$  Hz, 2 H) 5.0 (s, 1 H) 7.8 (m, 2 H) 7.9 (m, 2 H) 8.0 (m, 2 H) 8.1 (t,  $J=7.6$  Hz, 1 H) 8.2 (d,  $J=8.1$  Hz, 1 H) 8.2 (d,  $J=6.6$  Hz, 1 H) 9.0 (s, 1 H) 11.1 (s, 1 H).  $\text{EC}_{50}$  in primary enzyme assay 50  $\mu\text{M}$

**Example 2**

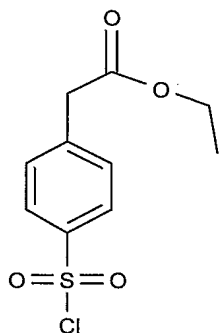
**Preparation of (R)-3-Cyclopentyl-2-[4-(4-methyl-piperazine-1-sulfonyl)-phenyl]-N-(5-morpholin-4-yl-thiazolo[5,4-b]pyridin-2-yl)-propionamide**

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#### A. Phenylacetic acid ethyl ester

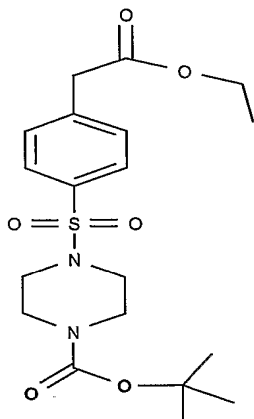
A solution of phenylacetic acid (50 g, 0.36 mol) in ethanol (150 mL) is treated with catalytic amount of sulfuric acid (4 mL). The reaction mixture is refluxed for 4 h. The reaction is then concentrated in vacuo. The residue is dissolved in diethyl ether (300 mL) and washed with saturated aqueous sodium bicarbonate solution (2 x 50 mL) and water (1 x 100 mL). The organic layer dried over sodium sulfate filtered and concentrated in vacuo to give phenylacetic acid ethyl ester as a colorless oil:  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  1.2 (t,  $J=7.2$ , 3H), 3.6 (s, 2H), 4.1 (q,  $J=7.2$ , 2H), 7.3 (m, 5H); MS 165  $[\text{M}+1]^+$ .



#### B. (4-Chlorosulfonyl-phenyl)-acetic acid ethyl ester

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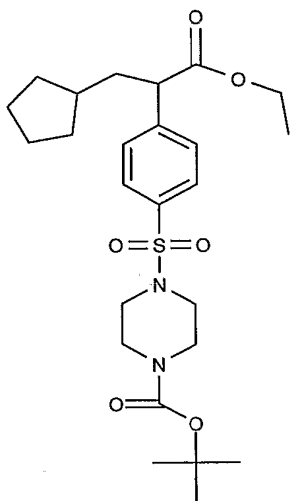
To 160mL of chlorosulfonic acid cooled to 0°C under nitrogen is added the title A compound, phenylacetic acid ethyl ester (59 g, 0.35 mol) over a period of 1 h. Reaction temperature is brought to RT (28°C), then stirred at ambient temperature for 18 h. The reaction is poured onto ice, extracted with ethyl acetate, dried over MgSO<sub>4</sub>, filtered and evaporated to a yellow oil and used directly in the next step.



**C. 4-(4-Ethoxycarbonylmethyl-benzenesulfonyl)-piperazine-1-carboxylic acid tert-butyl ester**

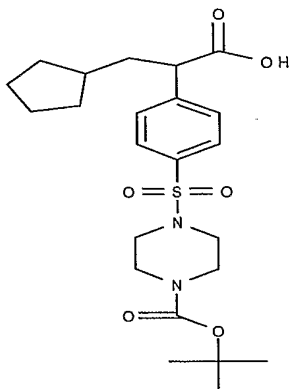
To a solution of N-BOC-piperazine (21.5 g, 0.114 mol) and DIEA (16.4 g, 22 mL, 0.13 mol) in 250 mL of DCM cooled to 0°C is added a solution of the title B compound, 4-chlorosulfonyl-phenyl)-acetic acid ethyl ester (30 g, 0.114 mol) in 50 mL of DCM within 30 min. The reaction mixture was stirred at ambient temperature for 18 h, and then evaporated to a crude solid. The residue is treated with 200mL of 1N HCl and extracted with ethyl acetate. The combined organic layer is washed with brine, sat. sodium carbonate and then with brine, dried with MgSO<sub>4</sub>, filtered and evaporated to a yellow oil which crystallized upon standing. This crude crystalline mass was recrystallized from MTBE to produce pure [4-(4-methyl-piperazine-1-sulfonyl)-phenyl]-acetic acid ethyl ester as a white solid.: <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ ppm 1.25 (t, 3 H, J = 7.1 Hz) 1.4 (s, 9 H) 3.0 (t, 4 H, J = 5 Hz) 3.5 (t, 4 H, J = 5 Hz) 3.7 (s, 2 H) 4.2 (q, J=7.1 Hz, 2 H) 7.5 (d, J=8.6 Hz, 2 H) 7.7 (d, 2 H, J = 8.6 Hz) MS 399 [M+1]<sup>+</sup>.

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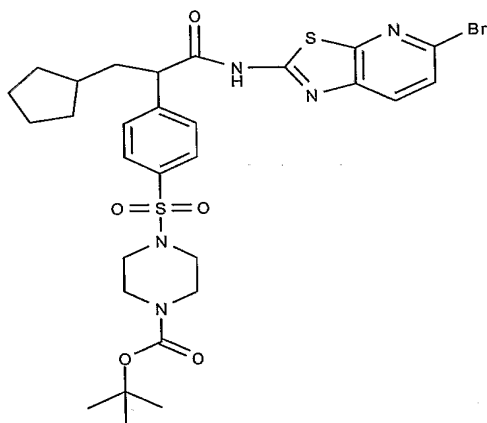
**D. 4-[4-(2-Cyclopentyl-1-ethoxycarbonyl-ethyl)-benzenesulfonyl]-piperazine-1-carboxylic acid tert-butyl ester**

LDA is freshly prepared from DIA (1.4mL, 10.0mmol) and 3.7 mL (9.2mmol) of 2.5 M nBuLi / hexanes in 50mL of THF at  $-78^{\circ}\text{C}$  under an inert atmosphere. Title compound C (3.6 g, 9.0mmol) in 15 mL of anhydrous THF is added dropwise and stirred for 1 h before the freshly prepared triflate of cyclopentylmethanol (2.5g, 10.5 mmol) in 15 mL of THF is added dropwise. The reaction is allowed to warm to ambient temperature and then is quenched into 100mL of 1N aqueous HCl. The mixture is extracted with ethyl acetate, washed with brine and the combined organic layer dried over  $\text{MgSO}_4$ , filtered and evaporated to afford product as a white solid:  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ )  $\delta$  ppm 1.06-1.15(m, 2H) 1.1 (t, 3 H,  $J = 7.1\text{Hz}$ ) 1.3 (s, 9H) 1.4 (m, 2 H) 1.6 (m, 4 H) 1.7 (m, 2 H) 2.0 (m, 1H) 2.8 (t, 4 H, 5 Hz) 3.4 (t, 4 H,  $J = 5\text{ Hz}$ ) 3.8 (t, 1 H  $J = 8\text{ Hz}$ ) 4.1 (q, 2 H,  $J = 7.1\text{ Hz}$ ) 7.6 (d, 2 H,  $J = 8.3\text{ Hz}$ ) 7.7 (d, 2 H,  $J = 8.3\text{ Hz}$ ) MS 493  $[\text{M}+1]^+$ .



**E. 3-Cyclopentyl-2-[4-(4-methyl-piperazine-1-sulfonyl)-phenyl]-propionic acid**

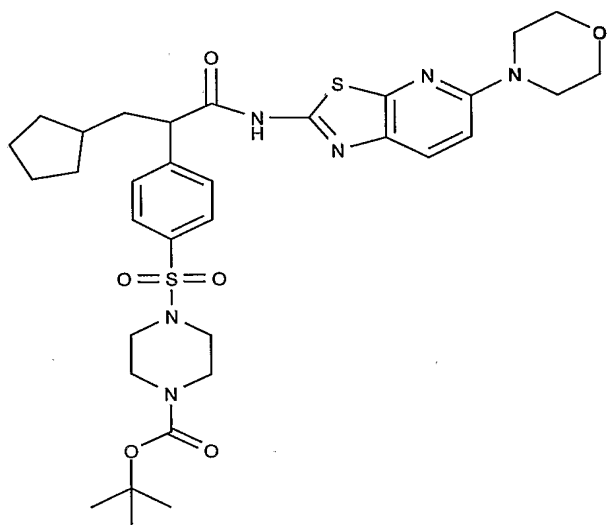
To a solution of the title D compound, 4-[4-(2-Cyclopentyl-1-ethoxycarbonyl-ethyl)-benzenesulfonyl]-piperazine-1-carboxylic acid tert-butyl ester (2.4 g, 5.1 mmol) in 25 mL of ethanol was added sodium hydroxide (0.6 g, 15 mmol) and the mixture stirred at ambient temperature for 15 h. The ethanol is then removed in vacuo at 45-50°C and the residue dissolved in water (25 mL) and extracted with ether (1 x 40 mL). The aqueous layer is acidified to pH 5 with 3 N aqueous hydrochloric acid solution and subsequently extracted with ethyl acetate. The combined organic layers were dried over MgSO<sub>4</sub>, filtered and evaporated to afford title compound E as a white solid: <sup>1</sup>H NMR (400 MHz, DMSO-D<sub>6</sub>) δ ppm 1.06-1.15(m, 2H) 1.3 (s, 9 H) 1.4 (m, 2 H) 1.6 (m, 3 H) 1.7 (m, 2 H) 2.0 (ddd, J=14.2, 7.0, 6.8 Hz, 1 H) 2.8 (t, 4 H, J = 5 Hz) 3.4 (t, 4H, J = 5 Hz) 3.68 (t, 1H, J = 8 Hz) 7.6 (d, J=8.3 Hz, 2 H) 7.7 (d, 2 H, J = 8.3 Hz) MS 421 [M-CO<sub>2</sub>]<sup>-</sup>.

**F. 4-{4-[1-(5-Bromo-thiazolo[5,4-b]pyridin-2-yl)carbamoyl]-2-cyclopentyl-ethyl}-benzenesulfonyl}-piperazine-1-carboxylic acid tert-butyl ester**

To a mixture of title compound E, 3-Cyclopentyl-2-[4-(4-methyl-piperazine-1-sulfonyl)-phenyl]-propionic acid (5.0g, 10.7 mmol), HOBt (2.8g, 20.7 mmol) and EDC (4.1g, 20.7 mmol) in 100 mL of DMF at 0°C was added 5.3 mL of DIEA, and the mixture is stirred for 30 min prior to addition of 5-Bromo-thiazolo[5,4-b]pyridin-2-yl amine (2.4g, 10.7mmol). The reaction mixture is stirred at ambient temperature for 18 h and then quenched into brine and extracted with ethyl acetate. The combined extracts were washed with 1N NaOH, brine and then dried over MgSO<sub>4</sub>. Filtration and evaporation then afforded a brownish foam which is purified by chromatography over silica to provide title compound F: <sup>1</sup>H NMR (400 MHz,

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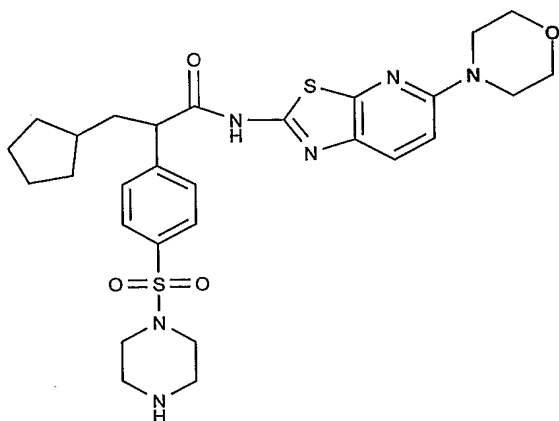
DMSO-D<sub>6</sub>)  $\delta$  ppm 1.06-1.17 (m, 2 H) 1.3 (s, 9 H) 1.37-1.46 (m, 2 H) 1.5-1.6 (m, 4 H) 1.68 (m, 2H) 1.77-1.84 (m, 1H) 2.8 (m, 4 H) 3.4 (m, 4H) 4.1 (t, 1H J = 8.4 Hz) 7.65-7.68 (m, 4 H) 7.72 (d, 1H, J = 8.5 Hz) 9.04 (d, 1H, J = 8.5 Hz) 12.9 (m, 1H);  $\delta$  1. MS 680 [M+1]<sup>+</sup>, 678[M-1]<sup>-</sup>,



**G. 4-{4-[2-Cyclopentyl-1-(5-morpholin-4-yl-thiazolo[5,4-b]pyridin-2-ylcarbamoyl)-ethyl]-benzenesulfonyl}-piperazine-1-carboxylic acid tert-butyl ester**

To title compound F, 4-{4-[1-(5-Bromo-thiazolo[5,4-b]pyridin-2-ylcarbamoyl)-2-cyclopentyl-ethyl]-benzenesulfonyl}-piperazine-1-carboxylic acid tert-butyl ester (0.1 g, 0.148 mmol) in a microwave vial was added Pd<sub>2</sub>dba<sub>3</sub> (0.013 g, 0.0148mmol), Xanphos (0.011g, 0.0295 mmol), sodium t-butoxide (0.028g, 0.295 mmol), morpholine (0.019g, 0.222 mmol), 2mL toluene and 1mL t-butanol. The sealed container was heated to 160°C for 5 minutes in a microwave reactor. Workup entailed quenching into water and extraction with ethyl acetate. The combined organic layer was dried over MgSO<sub>4</sub>, filtered and evaporated to afford a yellow oil. Purification on silica (EtOAc/hexane) afforded the product as an oil. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  1.12 (m, 2H) 1.39 (s, 9H) 1.48 (m, 2H) 1.62 (m, 3H) 1.73 (m, 2H) 1.90 (m, 1H) 2.24 (m, 1H) 3.01 (s, 4H) 3.51 (s, 4H) 3.54-3.58 (m, 4H) 3.65 (m, 1H) 3.80-3.87 (m, 4H) 6.73 (s, 1H) 7.50 (d, J = 8.34Hz, 2H) 7.73 (d, J = 8.08Hz, 3H) MS 685.3 [M+1]<sup>+</sup>.

**H. 3-Cyclopentyl-N-(5-morpholin-4-yl-thiazolo[5,4-b]pyridin-2-yl)-2-[4-(piperazine-1-sulfonyl)-phenyl]-propionamide**



Title compound G, 4-{4-[2-Cyclopentyl-1-(5-morpholin-4-yl-thiazolo[5,4-b]pyridin-2-ylcarbamoyl)-ethyl]-benzenesulfonyl}-piperazine-1-carboxylic acid tert-butyl ester (0.26g, 0.378 mmol) was dissolved in 5 mL DCM and 2 mL of TFA was added. The solution was stirred for 1 h and then evaporated to afford a crude oil. The residue was partitioned between 2N NaOH and ethyl acetate and extracted numerous times with ethyl acetate, dried over MgSO<sub>4</sub>, filtered and concentrated to afford a green solid. This material was taken on crude to the next reaction. <sup>1</sup>H NMR (400 MHz, DMSO)  $\delta$  1.07-1.16 (m, 2H) 1.39-1.50 (m, 2H) 1.52-1.63 (m, 3H) 1.68-1.79 (m, 3H) 2.16 (m, 1H) 2.71 (d, J = 4.80Hz, 4H) 2.76 (d, J = 5.05Hz, 4H) 3.43-3.51 (m, 4H) 3.67-3.74 (m, 4H) 4.07 (d, J = 8.84Hz, 1H) 6.97 (d, J = 9.09Hz, 1H) 7.64- 7.69 (m, 2H) 7.69- 7.73 (m, 2H) 7.88 (d, J = 9.09Hz, 1H) MS 585.31 [M+1]<sup>+</sup>.

**I. (R)-3-Cyclopentyl-2-[4-(4-methyl-piperazine-1-sulfonyl)-phenyl]-N-(5-morpholin-4-yl-thiazolo[5,4-b]pyridin-2-yl)-propionamide.**

Title compound H, 3-Cyclopentyl-N-(5-morpholin-4-yl-thiazolo[5,4-b]pyridin-2-yl)-2-[4-(piperazine-1-sulfonyl)-phenyl]-propionamide (0.21g, 0.354 mmol) was suspended in formaldehyde (2 mL) to which 1 mL of formic acid was added. The mixture was heated to 70°C for 7 h before being cooled and subsequently quenched into 2N NaOH and extracted with ethyl acetate. The combined organic layer was dried over MgSO<sub>4</sub>, filtered and evaporated to provide a brown foam which was purified over silica (0-20% EtOAc: methanol)

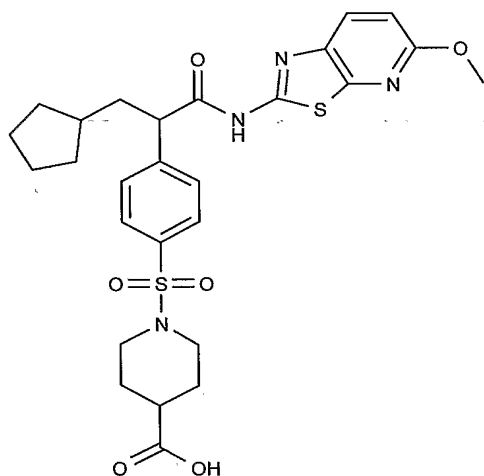


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to afford a white foam. This material was purified on a Chiracel column to afford pure (R)-3-Cyclopentyl-2-[4-(4-methyl-piperazine-1-sulfonyl)-phenyl]-N-(5-morpholin-4-yl-thiazolo[5,4-b]pyridin-2-yl)-propionamide as a white solid.  $^1\text{H}$  NMR (400 MHz, DMSO)  $\delta$  1.14 (m, 2H) 1.43 (d,  $J = 4.80\text{Hz}$ , 2H) 1.57 (d,  $J = 8.34\text{Hz}$ , 3H) 1.72 (d,  $J = 5.05\text{Hz}$ , 2H) 1.75-1.83 (m, 1H) 2.10 (s, 3H) 2.16 (m, 1H) 2.33 (d,  $J = 4.04\text{Hz}$ , 4H) 2.87 (s, 4H) 3.41-3.49 (m, 4H) 3.67-3.74 (m, 4H) 4.07 (t,  $J = 7.58\text{Hz}$ , 1H) 6.97 (d,  $J = 9.09\text{Hz}$ , 1H) 7.64-7.69 (m, 2H) 7.69-7.75 (m, 2H) 7.87 (d,  $J = 8.84\text{Hz}$ , 1H) MS 599.2  $[\text{M}+1]^+$ .

### Example 3

**1-{4-[2-Cyclopentyl-1-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)carbamoyl]-ethyl}-benzenesulfonyl}-piperidine-4-carboxylic acid**



#### A. 3-Cyclopentyl-2-(4-nitro-phenyl)-propionic acid ethyl ester

To a 1 L round bottom flask containing 250 mL of 9:1 THF/DMPU at  $-78^\circ\text{C}$  are added under nitrogen 11 mL (78.6 mmol) anhydrous DIEA followed by rapid addition of 32 mL of 2.5 M n-BuLi in hexanes. After 10 min at  $-78^\circ\text{C}$  a solution of 15.4 g (74 mmol) of p-nitrophenylacetic acid, ethyl ester in 100 mL of 9:1 THF/DMPU is added dropwise over 30 min. A deep purple solution results, and the reaction mixture is stirred at  $-78^\circ\text{C}$  for 30 min and then cyclopentyl methyl iodide (17.6 g, 78 mmol) in 50 mL of 9:1 THF/DMPU is added. The reaction is stirred while warming slowly to RT overnight. The mixture is poured into 1 L of 1 N HCl and

extracted twice with MTBE. The combined MTBE extracts are washed with brine, dried over anhydrous magnesium sulfate, filtered and reduced to an orange oil. Flash chromatography over silica eluting with 4:1 hexane/MTBE affords 3-cyclopentyl-2-(4-nitro-phenyl)-propionic acid ethyl ester as an orange oil:  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  1.0-1.1 (m, 2H), 1.2 (t, 3H,  $J=7.2$ ), 1.4-1.8 (m, 5H), 1.8-1.9 (m, 2H), 2.1-2.25 (m, 2H), 3.74 (t, 1H,  $J=7.8$ ), 4.1 (m, 2H), 7.51 (d, 2H,  $J=8.8$ ), 8.19 (d, 2H,  $J=8.8$ ); LC/MS 290 (M-1).

### B. 3-Cyclopentyl-2-(4-nitro-phenyl)-propionic acid

The title A compound, 3-cyclopentyl-2-(4-nitro-phenyl)-propionic acid ethyl ester (3.6 g, 12.3 mmol) is dissolved in 25 mL of methanol and aqueous NaOH (0.70 g, 17.5 mmol in 4 mL of water) is added and the mixture is stirred at RT overnight. The methanol is removed under reduced pressure and the residue is diluted with 100 mL of water and extracted with ether. The aqueous layer is then acidified with 1N HCl and then extracted with ethyl acetate. The combined ethyl acetate layers are dried over anhydrous magnesium sulfate, filtered and reduced under vacuum to a crude orange oil. The crude oil is triturated with 100 mL of hexane/10-15mL of ether to produce 3-cyclopentyl-2-(4-nitro-phenyl)-propionic acid as a solid:  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  1.0-1.1 (m, 2H), 1.4-1.8 (m, 5H), 1.8-1.9 (m, 2H), 2.1-2.25 (m, 2H), 3.74 (t, 1H,  $J=7.8$ ), 7.51 (d, 2H,  $J=8.8$ ), 8.19 (d, 2H,  $J=8.8$ ); LC/MS 218 ( $-\text{CO}_2$ , M-1), 279 ( $\text{M}+\text{NH}_4^+$ ).

### C. 3-Cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-2-(4-nitro-phenyl)-propionamide

The title B compound, 3-cyclopentyl-2-(4-nitro-phenyl)-propionic acid (7.5 g, 28.5 mmol) is dissolved in 25 mL of thionyl chloride and a drop of DMF and the mixture stirred at RT for 5-6 h. The excess of thionyl chloride is removed under reduced pressure. The residue is then taken up in DCM and added dropwise to a solution of the title E compound in Example 1, 5-methoxy-thiazolo[5,4-b]pyridin-2-ylamine (5.2 g, 28.5 mmol) in 25 mL of pyridine. The reaction mixture is stirred for 5 h before being evaporated to remove the pyridine. The residue is partitioned between ethyl acetate and brine, extracted with ethyl acetate. The combined organic layers are washed with saturated sodium bicarbonate, brine, dried over anhydrous magnesium sulfate, filtered and then reduced to an orange-brown solid. This is then vacuum dried to afford 3-cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-2-(4-nitro-phenyl)-propionamide as a foam:  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  1.0-1.1 (m, 2H), 1.4-1.8 (m, 5H), 1.8-1.9 (m, 2H), 2.1-2.25 (m, 2H), 3.6 (t, 1H,  $J=7.8$ ), 4.01 (s, 3H), 6.8 (d, 1H,  $J=8.8$ ),

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7.4 (d, 2H,  $J=8.6$ ), 7.8 (d, 1H,  $J=8.8$  Hz), 8.19 (d, 2H,  $J=8.6$  Hz), 9.3 (s, 1H); LC/MS 427 (M+1).

**D. 2-(4-Amino-phenyl)-3-cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide**

The title C compound, 3-cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-2-(4-nitro-phenyl)-propionamide (12 g, 28.2 mmol) is diluted with 160 mL of ethanol and 150 mL acetic acid. 8 g of iron powder (325 mesh, 0.14 mol) is added and the mixture heated to reflux. Once reflux begins the mixture is stirred vigorously and then heating is discontinued and the mixture is allowed to cool slowly. The solvents are removed and the residue is treated with 250 mL of water. Saturated sodium bicarbonate is added carefully to bring the mixture to a pH of 8-9. The mixture is extracted with ethyl acetate, washed with brine, dried and evaporated to give an orange solid which is triturated from hexane. The resulting solid is collected by filtration to afford 2-(4-amino-phenyl)-3-cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide:  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  1.0-1.1 (m, 2H), 1.4-1.8 (m, 5H), 1.8-1.9 (m, 2H), 2.1-2.25 (m, 2H), 3.6 (t, 1H,  $J=7.8$ ), 3.98 (s, 3H), 6.7 (d, 1H,  $J=8.8$ ), 6.8 (d, 2H,  $J=8.6$ ), 7.2 (d, 2H,  $J=8.6$ ), 7.8 (d, 1H,  $J=8.8$ ); LC/MS 397 (M+1).

**E. 4-[2-Cyclopentyl-1-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)carbamoyl]-ethyl]-benzenesulfonyl chloride**

The title D compound, 2-(4-amino-phenyl)-3-cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide (2.0 g, 5.1 mmol) is dissolved in 50 mL of acetic acid and 20 mL of concentrated HCl and the mixture is cooled to 0°C. A solution of 0.35 g (5.1 mmol) of  $\text{NaNO}_2$  in 5 mL of water is added dropwise and the mixture is stirred for 30 min. The resulting yellow solution is then added to 180 mL of a solution prepared by bubbling 74 g of sulfur dioxide gas into 740 mL of glacial acetic acid followed by addition of 30 g of  $\text{CuCl}_2$  in 35-40 mL water. The resulting mixture is filtered through filter paper to obtain a clear green solution) and the mixture is stirred at RT overnight (the initial black-green solution transforms to a light green solution after 24 h). The resulting mixture is poured onto 500 g of ice and the precipitated solids are collected by filtration, washed with water and then dissolved in ethyl acetate, washed with brine, dried over anhydrous magnesium sulfate, filtered and evaporated to afford a yellow foam. This material is flash chromatographed over silica eluting with 7:3 hexane/ethyl acetate to afford 4-[2-cyclopentyl-1-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)carbamoyl]-ethyl]-benzenesulfonyl chloride as a stable yellow foam:  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  1.0-1.1 (m, 2H), 1.4-1.8 (m, 5H), 1.8-1.9 (m, 2H), 2.1-2.25 (m, 2H), 3.7

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(t, 1H,  $J=7.8$ ), 4.01 (s, 3H), 6.8 (d, 1H,  $J=8.8$ ), 7.5 (d, 2H,  $J=8.6$ ), 7.8 (d, 1H,  $J=8.8$ ), 8.19 (d, 2H,  $J=8.6$ ), 9.3 (s, 1H); LC/MS 480 (M+1).

**F. 1-{4-[2-Cyclopentyl-1-(5-methoxy-thiazolo[5,4-b]pyridin-2-ylcarbamoyl)-ethyl]-benzenesulfonyl}-piperidine-4-carboxylic acid ethyl ester**

Title compound E, 4-[2-Cyclopentyl-1-(5-methoxy-thiazolo[5,4-b]pyridin-2-ylcarbamoyl)-ethyl]-benzenesulfonyl chloride (120 mg, 0.2499 mmol) was dissolved in dichloromethane. To this was added a solution of piperidine-4-carboxylic acid ethyl ester (38  $\mu$ L, 0.2499 mmol) and diisopropylethylamine (87  $\mu$ L, 0.4998 mmol) in dichloromethane. The reaction was stirred at room temperature for 1 hour, then concentrated. The residue was partitioned between 1N hydrochloric acid and ethyl acetate. The organic layer was separated, dried over anhydrous magnesium sulfate, filtered, and concentrated to afford a yellow oil. The crude was then purified via column chromatography 10-90% ethyl acetate in hexanes to afford the desired product as a yellow foam (107 mg, 71%).  $^1\text{H}$  NMR (400 MHz, CHLOROFORM- $d$ )  $\delta$  ppm 1.20 (t,  $J=7.07$  Hz, 3 H) 1.10 - 1.22 (m, 2 H) 1.50 (d,  $J=2.78$  Hz, 2 H) 1.49 (br. s., 1 H) 1.63 (dd,  $J=14.91$ , 7.83 Hz, 2 H) 1.62 (br. s., 1 H) 1.81 (dd,  $J=13.64$ , 3.79 Hz, 3 H) 1.95 (t,  $J=7.07$  Hz, 2 H) 1.91 (d,  $J=7.83$  Hz, 1 H) 2.21 - 2.31 (m, 2 H) 2.53 (td,  $J=11.43$ , 2.91 Hz, 2 H) 3.61 - 3.71 (m, 3 H) 4.00 (s, 3 H) 4.09 (q,  $J=7.07$  Hz, 2 H) 6.80 (d,  $J=8.84$  Hz, 1 H) 7.52 (d,  $J=8.59$  Hz, 2 H) 7.74 - 7.84 (m, 3 H) LC/MS 601.3 (M+1) 599.4 (M-1)

**G. 1-{4-[2-Cyclopentyl-1-(5-methoxy-thiazolo[5,4-b]pyridin-2-ylcarbamoyl)-ethyl]-benzenesulfonyl}-piperidine-4-carboxylic acid**

Sodium hydroxide (12 mg, 0.2996 mmol) was dissolved in a minimum amount of water and added to a solution of title compound F, 1-{4-[2-Cyclopentyl-1-(5-methoxy-thiazolo[5,4-b]pyridin-2-ylcarbamoyl)-ethyl]-benzenesulfonyl}-piperidine-4-carboxylic acid ethyl ester (90mg, 0.1498 mmol) in methanol. The reaction was stirred at room temperature overnight, poured into 1N hydrochloric acid, and extracted with ethyl acetate. Extracts were combined, dried over anhydrous magnesium sulfate, filtered, and concentrated to afford the title compound as a yellow foam (63 mg, 73%).  $^1\text{H}$  NMR (400 MHz, DMSO- $D_6$ )  $\delta$  ppm 1.05 - 1.16 (m, 2 H) 1.36 - 1.47 (m, 2 H) 1.49 - 1.61 (m, 5 H) 1.66 - 1.72 (m, 3 H) 1.75 (s, 1 H) 1.78 - 1.80 (m, 1 H) 1.92 - 2.02 (m, 1 H) 2.08 - 2.18 (m, 1 H) 2.40 (t,  $J=9.85$  Hz, 2 H) 3.35 (d,

$J=11.37$  Hz, 2 H) 3.82 - 3.92 (m, 4 H) 6.74 (d,  $J=8.59$  Hz, 1 H) 7.59 - 7.67 (m, 4 H) 7.79 (d,  $J=8.84$  Hz, 1 H) LC/MS 573.1 (M+1) 571.4 (M-1)  $EC_{50}$  in primary enzyme assay 7.1  $\mu$ M

#### **Example 4**

The following examples may be prepared by a skilled artisan using the methods described herein above.

4-1 3-Cyclopentyl-N-isoquinolin-1-yl-2-[4-(4-methyl-piperazine-1-sulfonyl)-phenyl]-propionamide: MS M+1 507,  $^1H$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  ppm 1.14 - 1.25 (m, 2 H) 1.41 - 1.51 (m, 2 H) 1.53 - 1.62 (m, 2 H) 1.67 - 1.78 (m, 2 H) 1.79 - 1.90 (m, 2 H) 2.18 - 2.27 (m, 1 H) 2.65 - 2.76 (m, 5 H) 2.88 (s, 1 H) 3.10 (br. s., 1 H) 3.41 (d,  $J=11.87$  Hz, 2 H) 3.76 (d,  $J=12.38$  Hz, 2 H) 4.96 (br. s., 1 H) 7.76 - 7.82 (m, 2 H) 7.86 - 7.91 (m, 2 H) 7.92 - 7.98 (m, 2 H) 8.06 (t,  $J=7.58$  Hz, 1 H) 8.16 (d,  $J=8.08$  Hz, 1 H) 8.22 (d,  $J=6.57$  Hz, 1 H) 9.00 (br. s., 1 H) 11.15 (br. s., 1 H).  $EC_{50}$  in primary enzyme assay 1.1  $\mu$ M

4-2 3-Cyclopentyl-N-(1-methyl-1H-benzimidazol-2-yl)-2-[4-(4-methyl-piperazine-1-sulfonyl)-phenyl]-propionamide: MS M+1 510,  $^1H$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  ppm 1.16 (t,  $J=7.07$  Hz, 2 H) 1.42 (br. s., 2 H) 1.56 (br. s., 2 H) 1.76 (dd,  $J=13.26, 7.20$  Hz, 3 H) 2.06 - 2.17 (m, 4 H) 2.32 (br. s., 4 H) 2.85 (br. s., 4 H) 3.29 (s, 3 H) 3.42 (br. s., 1 H) 3.54 (br. s., 2 H) 7.14 - 7.23 (m, 2 H) 7.42 (br. s., 2 H) 7.67 (t,  $J=7.96$  Hz, 4 H).

4-3 3-Cyclopentyl-2-[4-(4-methyl-piperazine-1-sulfonyl)-phenyl]-N-[1,3,4]thiadiazol-2-yl-propionamide: MS M+1 464,  $^1H$  NMR (400 MHz, DMSO- $D_6$ )  $\delta$  ppm 1.08 - 1.19 (m, 2 H) 1.38 - 1.48 (m, 2 H) 1.51 - 1.61 (m, 3 H) 1.64 - 1.75 (m, 2 H) 2.08 - 2.19 (m, 1 H) 2.11 (s, 3 H) 2.33 (s, 4H) 2.87 (s, 4H) 4.10 (t,  $J=7.8$  Hz, 1H) 7.65 (d,  $J=8.4$  Hz, 2 H) 7.72 (d,  $J=8.4$  Hz, 2 H) 9.17 (s, 1H).

4-4 3-Cyclopentyl-2-[4-(4-methyl-piperazine-1-sulfonyl)-phenyl]-N-quinolin-2-yl-propionamide: MS M+1 507,  $^1H$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  ppm 1.11 - 1.22 (m, 2 H) 1.15 (dd,  $J=11.62, 6.06$  Hz, 1 H) 1.44 (dd,  $J=7.20, 4.42$  Hz, 1 H) 1.56 (dd,  $J=11.62, 3.28$  Hz, 1 H) 1.52 - 1.59 (m, 1 H) 1.73 (dt,  $J=13.14, 6.57$  Hz, 2 H) 2.18 (ddd,  $J=12.95, 8.53, 6.57$  Hz, 1 H) 2.56 - 2.67 (m, 2 H) 2.70 (d,  $J=3.79$  Hz, 3 H) 3.13 (br. s., 2 H) 3.41 (d,  $J=11.62$  Hz, 2 H) 3.74 (d,  $J=12.13$  Hz, 2 H) 4.13 (d,  $J=3.28$  Hz, 1 H) 7.49 (dd,  $J=15.03, 1.14$  Hz, 1 H) 7.69 - 7.80

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(m, 2 H) 7.76 (d, J=2.02 Hz, 3 H) 7.90 (d, J=7.58 Hz, 1 H) 8.23 - 8.30 (m, 1 H) 8.32 - 8.37 (m, 1 H) 10.35 (br. s., 1 H) 11.23 (s, 1 H).

4-5 N-(6-Chloro-pyridazin-3-yl)-3-cyclopentyl-2-[4-(4-methyl-piperazine-1-sulfonyl)-phenyl]-propionamide: MS M+1 493, <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm 1.20 (d, J=6.32 Hz, 1 H) 1.27 (br. s., 1 H) 1.40 - 1.52 (m, 1 H) 1.43 (d, J=4.55 Hz, 1 H) 1.56 (br. s., 2 H) 1.62 (d, J=7.58 Hz, 1 H) 1.73 (dd, J=13.14, 6.82 Hz, 3 H) 2.13 (dd, J=6.69, 1.89 Hz, 1 H) 2.53 (br. s., 2 H) 2.66 - 2.77 (m, 3 H) 3.12 (br. s., 2 H) 3.42 (br. S., 2H) 3.73 (br. s., 2 H) 4.18 (t, J=7.45 Hz, 1 H) 4.13 (dd, J=5.56, 3.28 Hz, 1 H) 7.67 - 7.78 (m, 4 H) 7.85 (d, J=9.60 Hz, 1 H) 8.37 (d, J=9.35 Hz, 1 H) 9.87 (br. s., 1 H) 11.68 (s, 1 H).

4-6 3-Cyclopentyl-2-[4-(4-methyl-piperazine-1-sulfonyl)-phenyl]-N-(5-methyl-thiazol-2-yl)-propionamide: MS M+1 477, <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm 1.14 (t, J=10.99 Hz, 2 H) 1.12 (br. s., 1 H) 1.44 (dd, J=7.33, 4.55 Hz, 2 H) 1.57 (dq, J=14.75, 7.46 Hz, 2 H) 1.52 - 1.62 (m, 2 H) 1.66 - 1.77 (m, 1 H) 1.73 (dd, J=13.26, 6.44 Hz, 2 H) 2.15 (ddd, J=13.39, 8.46, 7.20 Hz, 1 H) 2.32 (d, J=1.26 Hz, 3 H) 2.77 (s, 3 H) 3.15 (br. s., 2 H) 3.43 (br. s., 2 H) 3.75 (br. s., 2 H) 4.05 (dd, J=8.46, 6.69 Hz, 1 H) 7.13 (d, J=1.26 Hz, 1 H) 7.66 - 7.72 (m, 2 H) 7.74 - 7.79 (m, 2 H) 12.26 (s, 1 H).

4-7 2-{3-Cyclopentyl-2-[4-(4-methyl-piperazine-1-sulfonyl)-phenyl]-propionylamino}-thiazole-4-carboxylic acid: MS M+1 507, <sup>1</sup>H NMR (400 MHz, DMSO-D<sub>6</sub>) δ ppm 1.02 - 1.13 (m, 2 H) 1.34 - 1.44 (m, 2 H) 1.50 - 1.58 (m, 2 H) 1.58 - 1.63 (m, 1 H) 1.64 - 1.69 (m, 2 H) 2.00 - 2.09 (m, 1 H) 2.10 (s, 2 H) 2.33 (d, J=4.29 Hz, 4 H) 2.85 (s, 4 H) 3.57 (t, J=7.45 Hz, 1 H) 6.73 (s, 1H) 7.57 (d, J=8.4 Hz, 2 H) 7.63 (d, J=8.4 Hz, 2 H).

4-8 2-[3-Cyclopentyl-2-(4-diethylsulfamoyl-phenyl)-propionylamino]-6,7-dihydro-4H-thiazolo[5,4-c]pyridine-5-carboxylic acid tert-butyl ester: MS M+1 591, <sup>1</sup>H NMR (400 MHz, CHLOROFORM-d) δ ppm 1.15 (t, J=7.07 Hz, 7 H) 1.07 - 1.17 (m, 1 H) 1.47 (s, 8 H) 1.57 - 1.65 (m, 6 H) 1.67 - 1.77 (m, 2 H) 1.88 (t, J=14.02 Hz, 1 H) 2.22 (dt, J=13.64, 7.45 Hz, 1 H) 2.69 (br. s., 2 H) 3.24 (q, J=7.16 Hz, 4 H) 3.63 (t, J=7.58 Hz, 1 H) 3.67 - 3.75 (m, 2 H) 4.54 (s, 2 H) 7.44 (d, J=8.59 Hz, 2 H) 7.78 (d, J=8.34 Hz, 2 H) 8.72 (br. s., 1 H). EC<sub>50</sub> in primary enzyme assay 0.095μM

4-9 3-Cyclopentyl-2-(4-diethylsulfamoyl-phenyl)-N-(4,5,6,7-tetrahydro-thiazolo[5,4-c]pyridin-2-yl)-propionamide: MS M+1 491, <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm 1.03 (t, J=7.07 Hz, 6 H) 1.12 (d, J=19.96 Hz, 1 H) 1.11 (d, J=8.34 Hz, 1 H) 1.43 (dd, J=7.20, 4.67 Hz, 2 H) 1.51 - 1.60 (m, 1 H) 1.56 (t, J=7.58 Hz, 2 H) 1.73 (dt, J=13.20, 6.66 Hz, 2 H) 1.65 (d, J=1.01 Hz, 1 H) 2.12 (dd, J=6.95, 4.67 Hz, 1 H) 2.85 (br. s., 2 H) 3.14 (q, J=7.07 Hz, 4 H) 3.40 (br. s., 2 H) 4.03 (dd, J=8.59, 6.57 Hz, 1 H) 4.27 (br. s., 2 H) 7.58 (d, J=8.34 Hz, 2 H) 7.77 (d, J=8.34 Hz, 2 H) 9.39 (br. s., 1 H) 12.52 (s, 1 H).

4-10 3-Cyclopentyl-2-(4-diethylsulfamoyl-phenyl)-N-(5-methyl-4,5,6,7-tetrahydro-thiazolo[5,4-c]pyridin-2-yl)-propionamide: MS M+1 505, <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm 1.03 (t, J=7.07 Hz, 6 H) 1.14 (br. s., 1 H) 1.11 (d, J=11.62 Hz, 2 H) 1.42 (d, J=5.05 Hz, 2 H) 1.51 - 1.62 (m, 3 H) 1.73 (dd, J=13.52, 6.69 Hz, 3 H) 2.12 (dt, J=8.34, 6.82 Hz, 1 H) 2.91 (br. s., 4 H) 3.14 (q, J=7.07 Hz, 4 H) 3.64 (br. s., 1 H) 4.02 (dd, J=8.46, 6.44 Hz, 1 H) 4.26 (br. s., 1 H) 4.51 (br. s., 1 H) 7.58 (d, J=8.34 Hz, 2 H) 7.77 (d, J=8.34 Hz, 2 H) 10.59 (br. s., 1 H) 12.55 (s, 1 H).

4-11 3-Cyclopentyl-2-(4-diethylsulfamoyl-phenyl)-N-pyrazin-2-yl-propionamide: MS M+1 431, <sup>1</sup>H NMR (400 MHz, CHLOROFORM-d) δ ppm 1.13 (q, J=7.24 Hz, 6 H) 1.45 - 1.54 (m, 2 H) 1.49 (dd, J=7.58, 4.80 Hz, 2 H) 1.63 (td, J=7.52, 3.41 Hz, 2 H) 1.70 (d, J=7.33 Hz, 1 H) 1.89 (dd, J=13.64, 7.33 Hz, 1 H) 2.22 (t, J=6.82 Hz, 1 H) 3.24 (q, J=7.07 Hz, 4 H) 3.67 (t, J=7.58 Hz, 1 H) 7.51 (d, J=8.34 Hz, 2 H) 7.79 (d, J=8.59 Hz, 2 H) 8.10 (s, 1 H) 8.18 (d, J=1.77 Hz, 1 H) 8.34 (d, J=2.53 Hz, 1 H) 9.54 (s, 1 H).

4-12 3-Cyclopentyl-2-(4-diethylsulfamoyl-phenyl)-N-pyridin-2-yl-propionamide: MS M+1 430, <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm 1.01 (t, J=7.20 Hz, 6 H) 1.07 - 1.17 (m, 2 H) 1.42 (dd, J=7.33, 4.55 Hz, 2 H) 1.52 - 1.61 (m, 3 H) 1.67 (ddd, J=13.26, 6.82, 6.69 Hz, 3 H) 2.11 (ddd, J=12.95, 8.78, 6.32 Hz, 1 H) 3.12 (q, J=7.07 Hz, 4 H) 4.07 (dd, J=8.46, 6.44 Hz, 1 H) 7.08 (ddd, J=6.69, 5.43, 1.01 Hz, 1 H) 7.61 (d, J=8.34 Hz, 2 H) 7.71 - 7.77 (m, 1 H) 7.74 (d, J=8.59 Hz, 2 H) 8.05 (d, J=8.34 Hz, 1 H) 8.28 (dd, J=4.80, 1.01 Hz, 1 H) 10.78 (s, 1 H).

4-13 3-Cyclopentyl-2-(4-diethylsulfamoyl-phenyl)-N-(6-trifluoromethyl-pyridin-2-yl)-propionamide: MS M+1 498, <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm 1.02 (q, J=7.07 Hz, 6 H) 1.06 - 1.16 (m, J=11.40, 7.63, 7.63, 3.41 Hz, 2 H) 1.42 (dd, J=7.20, 4.67 Hz, 2 H) 1.51 - 1.62 (m, 1 H) 1.55 (td, J=8.97, 7.07 Hz, 2 H) 1.69 (ddd, J=13.14, 6.95, 6.69 Hz, 3 H) 2.12 (ddd,

J=13.20, 8.27, 6.82 Hz, 1 H) 3.12 (q, J=7.07 Hz, 4 H) 4.13 (dd, J=8.21, 6.69 Hz, 1 H) 7.61 (d, J=8.34 Hz, 2 H) 7.57 (d, J=7.33 Hz, 1 H) 7.75 (d, J=8.59 Hz, 2 H) 8.04 (t, J=7.96 Hz, 1 H) 8.35 (d, J=8.59 Hz, 1 H) 11.21 (s, 1 H).

4-14 3-Cyclopentyl-2-(4-diethylsulfamoyl-phenyl)-N-pyrimidin-2-yl-propionamide: MS M+1 431, <sup>1</sup>H NMR (400 MHz, CHLOROFORM-d) δ ppm 1.12 - 1.17 (m, 8 H) 1.48 (d, J=7.33 Hz, 3 H) 1.72 (d, J=11.62 Hz, 2 H) 1.68 (br. s., 1 H) 1.85 (dd, J=13.52, 7.20 Hz, 2 H) 2.26 (t, J=14.02 Hz, 1 H) 2.26 (d, J=13.39 Hz, 1 H) 3.22 (d, J=7.07 Hz, 4 H) 3.20 (s, 1 H) 7.01 (t, J=4.80 Hz, 1 H) 7.55 (d, J=8.34 Hz, 2 H) 7.75 (d, J=8.34 Hz, 2 H) 8.58 (d, J=4.80 Hz, 2 H).

4-15 3-Cyclopentyl-2-(4-diethylsulfamoyl-phenyl)-N-thiazol-2-yl-propionamide: MS M+1 436, <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm 1.02 (t, J=7.07 Hz, 5 H) 1.10 (ddd, J=19.77, 8.15, 3.66 Hz, 1 H) 1.42 (td, J=7.52, 3.16 Hz, 2 H) 1.49 - 1.60 (m, 1 H) 1.55 (d, J=5.05 Hz, 2 H) 1.65 - 1.76 (m, 1 H) 1.71 (dd, J=13.26, 6.69 Hz, 2 H) 2.13 (ddd, J=13.33, 8.53, 6.95 Hz, 1 H) 3.12 (q, J=7.16 Hz, 4 H) 3.31 (s, 2 H) 4.02 (dd, J=8.46, 6.69 Hz, 1 H) 7.20 (d, J=3.54 Hz, 1 H) 7.45 (d, J=3.54 Hz, 1 H) 7.58 (d, J=8.34 Hz, 2 H) 7.75 (d, J=8.34 Hz, 2 H) 12.41 (s, 1 H).  
EC<sub>50</sub> in primary enzyme assay 0.06 μM

4-16 6-[3-Cyclopentyl-2-(4-diethylsulfamoyl-phenyl)-propionylamino]-nicotinic acid: MS M+1 474, <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm 1.01 (t, J=7.07 Hz, 6 H) 1.13 (m, 2H) 1.42 (br. s., 2 H) 1.55 (br. s., 3 H) 1.65 (d, J=19.20 Hz, 3 H) 2.11 (br. s., 1 H) 3.11 (q, J=6.82 Hz, 4 H) 4.05 (br. s., 1 H) 7.59 - 7.64 (m, 2 H) 7.73 (d, J=8.34 Hz, 2 H) 7.90 (d, J=9.09 Hz, 1 H) 8.02 (d, J=8.34 Hz, 1 H) 8.63 (s, 1 H) 10.73 (s, 1 H).

4-17 3-Cyclopentyl-2-[4-(4-methyl-piperazine-1-sulfonyl)-phenyl]-N-(1H-tetrazol-5-yl)-propionamide: MS M+1 448.

4-18 N-(5-Chloro-thiazol-2-yl)-3-cyclopentyl-2-[4-(4-methyl-piperazine-1-sulfonyl)-phenyl]-propionamide: MS M+1 497, <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm 1.08 - 1.19 (m, 2 H) 1.42 (br. s., 1 H) 1.44 (dd, J=7.20, 4.67 Hz, 1 H) 1.51 - 1.61 (m, 3 H) 1.68 (br. s., 1H) 1.73 (d, J=12.13 Hz, 1 H) 1.75 - 1.81 (m, 1 H) 2.09 - 2.19 (m, 1 H) 2.76 (s, 3 H) 3.15 (br. s., 2 H) 3.43 (br. s., 2 H) 3.75 (br. s., 2 H) 4.07 (t, J=7.45 Hz, 1 H) 7.52 (s, 1 H) 7.69 (d, J=8.34 Hz, 2 H) 7.75 - 7.79 (m, 2 H) 12.73 (s, 1 H).



4-19 3-Cyclopentyl-2-[4-(4-methyl-piperazine-1-sulfonyl)-phenyl]-N-(4-methyl-thiazol-2-yl)-propionamide: MS M+1 477, <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ ppm - 1.13 (d, *J*=3.03 Hz, 2 H) 1.44 (dd, *J*=7.20, 4.67 Hz, 2 H) 1.52 - 1.61 (m, 3 H) 1.66 - 1.77 (m, 3 H) 2.16 (ddd, *J*=13.26, 8.72, 7.07 Hz, 1 H) 2.24 (d, *J*=1.01 Hz, 3 H) 2.29 - 2.37 (m, 1 H) 2.77 (s, 3 H) 3.15 (br. s., 2 H) 3.44 (br. s., 1 H) 3.49 (br. s., 1 H) 3.74 (br. s., 2 H) 4.04 (dd, *J*=8.59, 6.57 Hz, 1 H) 6.75 (d, *J*=1.01 Hz, 1 H) 7.63 - 7.72 (m, 2 H) 7.74 - 7.79 (m, 2 H) 9.34 (br. s., 1 H) 12.39 (br. s., 1 H).

4-20 3-Cyclopentyl-N-(1H-indazol-3-yl)-2-[4-(4-methyl-piperazine-1-sulfonyl)-phenyl]-propionamide: MS M+1 496, <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ ppm -1.11 - 1.22 (m, 2 H) 1.42 (dd, *J*=7.33, 3.79 Hz, 2 H) 1.52 - 1.59 (m, 3 H) 1.63 - 1.72 (m, 4 H) 1.84 (dt, *J*=13.39, 6.69 Hz, 1 H) 2.21 - 2.30 (m, 1 H) 2.74 (s, 3 H) 3.13 (br. s., 2 H) 3.52 (br. s., 8 H) 3.74 (br. s., 2 H) 5.16 (dd, *J*=8.34, 6.82 Hz, 1 H) 6.58 (br. s., 1 H) 7.35 (t, *J*=7.58 Hz, 1 H) 7.53 - 7.58 (m, 1 H) 7.72 - 7.78 (m, 4 H) 7.89 (d, *J*=7.83 Hz, 1 H) 8.26 (d, *J*=8.34 Hz, 1 H) 9.28 (br. s., 1 H).

4-21 3-Cyclopentyl-2-[4-(4-methyl-piperazine-1-sulfonyl)-phenyl]-N-(5-trifluoromethyl-[1,3,4]thiadiazol-2-yl)-propionamide: MS M+1 533, <sup>1</sup>H NMR (400 MHz, DMSO-*D*<sub>6</sub>) δ ppm 1.08 - 1.19 (m, 2 H) 1.43 (dd, *J*=7.20, 4.67 Hz, 2 H) 1.51 - 1.62 (m, 3 H) 1.64 - 1.74 (m, 2 H) 1.81 - 1.87 (m, 2 H) 2.11 - 2.21 (m, 4 H) 2.40 (s, 4 H) 2.73 (s, 3 H) 2.89 (s, 4 H) 7.64 (d, *J*=8.3 Hz, 2 H) 7.73 (d, *J*=8.3 Hz, 2 H) 7.95 (s, 1 H).

4-22 N-(5-Bromo-thiazolo[5,4-*b*]pyridin-2-yl)-3-cyclopentyl-2-[4-(4-methyl-piperazine-1-sulfonyl)-phenyl]-propionamide: MS M+1 594, <sup>1</sup>H NMR (400 MHz, DMSO-*D*<sub>6</sub>) δ ppm 1.07 - 1.19 (m, 2 H) 1.39 - 1.49 (m, 2 H) 1.52 - 1.63 (m, 3 H) 1.66 - 1.76 (m, 2 H) 1.79-1.86 (m, 1 H) 2.09 - 2.19 (m, 4 H) 2.33 (s, 4 H) 2.87 (s, 4 H) 7.65 - 7.70 (m, 3 H) 7.71 - 7.75 (m, 2 H) 8.06 (d, *J*=8.5 Hz, 1 H). EC<sub>50</sub> in primary enzyme assay 0.39 μM

4-23 6-{3-Cyclopentyl-2-[4-(4-methyl-piperazine-1-sulfonyl)-phenyl]-propionylamino}-nicotinic acid: MS M+1 501, <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ ppm 1.07 - 1.18 (m, 2 H) 1.43 (dd, *J*=7.20, 4.67 Hz, 2 H) 1.51 - 1.62 (m, 3 H) 1.64 - 1.74 (m, 3 H) 2.06 - 2.16 (m, 4 H) 2.31 (t, *J*=4.55 Hz, 5 H) 2.85 (br. s., 4 H) 4.08 (d, *J*=7.33 Hz, 1 H) 7.64 - 7.71 (m, 4 H) 7.91 (d, *J*=8.59 Hz, 1 H) 8.03 (dd, *J*=8.46, 2.15 Hz, 1 H) 8.64 (d, *J*=1.26 Hz, 1 H) 10.76 (s, 1 H). EC<sub>50</sub> in primary enzyme assay 1.4 μM

4-24 (2-{3-Cyclopentyl-2-[4-(4-methyl-piperazine-1-sulfonyl)-phenyl]-propionylamino}-thiazol-4-yl)-acetic acid ethyl ester: MS M+1 549, <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ ppm 1.04 - 1.15 (m, 5 H) 1.40 (dd, *J*=7.07, 4.55 Hz, 2 H) 1.47 - 1.57 (m, 3 H) 1.62 - 1.73 (m, 3 H) 2.05 - 2.15 (m, 4 H) 2.28 (t, *J*=4.55 Hz, 4 H) 2.83 (br. s., 4 H) 3.26 (s, 9 H) 3.26 (s, 6 H) 3.62 (s, 2 H) 3.95 - 4.05 (m, 1 H) 6.94 (s, 1 H) 7.56 - 7.61 (m, 2 H) 7.65 - 7.69 (m, 2 H) 12.46 (s, 1 H).

4-25 N-Benzothiazol-2-yl-3-cyclopentyl-2-[4-(4-methyl-piperazine-1-sulfonyl)-phenyl]-propionamide: MS M+1 513, <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ ppm 1.19 - 1.30 (m, 2 H) 1.54 (dd, *J*=6.95, 4.42 Hz, 2 H) 1.62 - 1.74 (m, 3 H) 1.85 (br. s., 2 H) 1.90 (ddd, *J*=13.52, 6.95, 6.82 Hz, 1 H) 2.23 - 2.34 (m, 1 H) 2.82 - 2.88 (m, 3 H) 3.24 (br. s., 2 H) 3.52 (br. s., 2 H) 3.84 (br. s., 2 H) 4.19 - 4.27 (m, 1 H) 7.38 - 7.43 (m, 1 H) 7.50 - 7.56 (m, 1 H) 7.80 - 7.85 (m, 3 H) 7.86 - 7.90 (m, 2 H) 8.06 (d, *J*=7.33 Hz, 1 H) 9.36 (br. s., 1 H) 12.82 (s, 1 H).

4-26 N-(6-Bromo-benzothiazol-2-yl)-3-cyclopentyl-2-[4-(4-methyl-piperazine-1-sulfonyl)-phenyl]-propionamide: MS M+1 593, <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ ppm 1.01 - 1.13 (m, 2 H) 1.30 - 1.41 (m, 2 H) 1.44 - 1.55 (m, 3 H) 1.57 - 1.64 (m, 2 H) 1.72 (ddd, *J*=13.58, 7.07, 6.88 Hz, 1 H) 2.09 (dt, *J*=13.20, 7.80 Hz, 1 H) 2.67 (s, 3 H) 3.06 (br. s., 2 H) 3.34 (br. s., 2 H) 3.67 (br. s., 2 H) 4.05 (t, *J*=7.58 Hz, 1 H) 7.49 (dd, *J*=8.59, 2.02 Hz, 1 H) 7.57 - 7.60 (m, 1 H) 7.61 - 7.66 (m, 2 H) 7.68 - 7.72 (m, 2 H) 8.16 (d, *J*=2.02 Hz, 1 H) 9.28 (br. s., 1 H) 12.75 (s, 1 H).

4-27 3-Cyclopentyl-N-(6-methanesulfonyl-benzothiazol-2-yl)-2-[4-(4-methyl-piperazine-1-sulfonyl)-phenyl]-propionamide: MS M+1 591, <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ ppm 1.17 (br. s., 2 H) 1.46 (d, *J*=7.83 Hz, 2 H) 1.60 (br. s., 3 H) 1.77 (s, 2 H) 1.80 - 1.90 (m, 1 H) 2.21 (d, *J*=12.88 Hz, 1 H) 2.77 (br. s., 3 H) 3.26 (s, 3 H) 3.45 (br. s., 2 H) 3.77 (br. s., 3 H) 4.18 (t, *J*=7.58 Hz, 1 H) 7.72 - 7.78 (m, 2 H) 7.78 - 7.83 (m, 2 H) 7.93 - 7.99 (m, 2 H) 8.65 (s, 1 H) 9.32 (br. s., 1 H) 13.06 (s, 1 H).

4-28 3-Cyclopentyl-2-[4-(4-methyl-piperazine-1-sulfonyl)-phenyl]-N-(5-phenoxy-thiazolo[5,4-*b*]pyridin-2-yl)-propionamide: MS M+1 606, <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ ppm 1.07 - 1.18 (m, 2 H) 1.43 (dd, *J*=7.07, 4.55 Hz, 2 H) 1.51 - 1.62 (m, 3 H) 1.70 (br. s., 1 H) 1.77 (td, *J*=13.26, 6.32 Hz, 1 H) 2.09 - 2.20 (m, 1 H) 2.57 (br. s., 2 H) 2.72 (br. s., 3 H) 3.11 (br. s., 2 H) 3.42 (br. s., 2 H) 3.73 (br. s., 2 H) 4.14 (t, *J*=7.45 Hz, 1 H) 7.08 - 7.17 (m, 3 H) 7.22 (t,

$J=7.45$  Hz, 1 H) 7.39 - 7.46 (m, 2 H) 7.68 - 7.79 (m, 4 H) 8.16 (d,  $J=8.84$  Hz, 1 H) 10.01 (br. s., 1 H) 12.81 (s, 1 H).

4-29 2-{3-Cyclopentyl-2-[4-(4-methyl-piperazine-1-sulfonyl)-phenyl]-propionylamino}-thiazol-4-yl)-acetic acid: MS M+1 521,  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  ppm 1.09 (br. s., 2 H) 1.33 - 1.42 (m, 2 H) 1.47 - 1.56 (m, 3 H) 1.64 - 1.75 (m, 3 H) 2.03 - 2.13 (m, 4 H) 2.26 - 2.36 (m, 4 H) 2.85 (br. s., 4 H) 3.22 (br. s., 2 H) 4.52 (br. s., 1 H) 6.60 (br. s., 1 H) 7.64 (d,  $J=8.34$  Hz, 2 H) 7.67 - 7.77 (m, 2 H).

4-30 2-{3-Cyclopentyl-2-[4-(4-methyl-piperazine-1-sulfonyl)-phenyl]-propionylamino}-benzothiazole-6-carboxylic acid ethyl ester: MS M+1 585;  $^1\text{H}$  NMR (400 MHz, CHLOROFORM- $d$ )  $\delta$  ppm 1.09 - 1.20 (m, 2 H) 1.42 (t,  $J=7.07$  Hz, 3 H) 1.46 - 1.56 (m, 2 H) 1.58 - 1.69 (m, 4 H) 1.69 - 1.81 (m, 8 H) 1.87 - 1.98 (m, 1 H) 2.23 - 2.30 (m, 4 H) 2.48 (t,  $J=4.80$  Hz, 4 H) 3.05 (br. s., 4 H) 3.74 (t,  $J=7.58$  Hz, 1 H) 4.41 (q,  $J=7.24$  Hz, 2 H) 7.46 - 7.53 (m, 2 H) 7.68 - 7.76 (m, 3 H) 8.12 (dd,  $J=8.59$ , 1.77 Hz, 1 H) 8.54 (d,  $J=1.26$  Hz, 1 H) 9.23 (br. s., 1 H).

4-31 2-{3-Cyclopentyl-2-[4-(4-methyl-piperazine-1-sulfonyl)-phenyl]-propionylamino}-benzothiazole-6-carboxylic acid: MS M+1 557,  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  ppm 1.09 - 1.18 (m, 1 H) 1.42 (dd,  $J=7.20$ , 4.93 Hz, 2 H) 1.54 (d,  $J=7.33$  Hz, 1 H) 1.60 (d,  $J=7.07$  Hz, 2 H) 1.70 (d,  $J=3.03$  Hz, 1 H) 1.72 (d,  $J=6.82$  Hz, 2 H) 2.10 (s, 4 H) 2.32 (t,  $J=4.29$  Hz, 4 H) 2.86 (br. s., 4 H) 3.79 (br. s., 1 H) 7.31 (br. s., 1 H) 7.64 (s, 4 H) 7.75 (br. s., 1 H) 8.13 (br. s., 3 H).

4-32 2-((R)-3-Cyclopentyl-2-[4-(4-methyl-piperazine-1-sulfonyl)-phenyl]-propionylamino)-benzothiazole-6-carboxylic acid: MS M+1 558,  $^1\text{H}$  NMR (400 MHz, DMSO- $D_6$ )  $\delta$  ppm 1.06 - 1.17 (m, 2 H) 1.36 - 1.47 (m, 2 H) 1.51 - 1.62 (m, 3 H) 1.66 - 1.74 (m, 3 H) 2.07 - 2.17 (m, 4 H) 2.26 - 2.36 (m, 4 H) 2.86 (s, 4 H) 7.27 (d,  $J=8.1$  Hz, 1H) 7.60 - 7.67 (m, 4 H) 7.74 (d,  $J=8.08$  Hz, 1 H).

4-33 2-{3-Cyclopentyl-2-[4-(4-methyl-piperazine-1-sulfonyl)-3-trifluoromethyl-phenyl]-propionylamino}-benzothiazole-6-carboxylic acid: : MS M+1 625,  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  ppm 1.16 (d,  $J=8.08$  Hz, 2 H) 1.45 (br. s., 1 H) 1.44 (d,  $J=5.05$  Hz, 1 H) 1.52 - 1.63 (m, 1 H) 1.58 (d,  $J=8.59$  Hz, 2 H) 1.74 (d,  $J=12.63$  Hz, 2 H) 1.74 (br. s., 1 H) 1.85 (ddd,  $J=13.52$ ,

6.95, 6.82 Hz, 1 H) 2.23 (dd,  $J=15.54, 13.52$  Hz, 1 H) 2.80 (br. s., 3 H) 3.05 (br. s., 3 H) 3.31 (br. s., 2 H) 3.84 (br. s., 2 H) 4.23 (t,  $J=7.45$  Hz, 1 H) 7.80 (d,  $J=8.59$  Hz, 1 H) 7.96 (dd,  $J=8.34, 1.52$  Hz, 1 H) 8.00 (dd,  $J=8.59, 1.77$  Hz, 1 H) 8.08 (d,  $J=1.52$  Hz, 1 H) 8.12 (d,  $J=8.34$  Hz, 1 H) 8.61 (d,  $J=1.52$  Hz, 1 H) 12.95 (s, 1 H).

4-34 2-[(R)-3-Cyclopentyl-2-[4-(4-methyl-piperazine-1-sulfonyl)-phenyl]-propionylamino]-benzothiazole-6-carboxylic acid (2-methoxy-ethyl)-amide: MS  $M+1$  614,  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ )  $\delta$  ppm 1.16 (d,  $J=12.13$  Hz, 2 H) 1.45 (br. s., 2 H) 1.62 (d,  $J=7.83$  Hz, 2 H) 1.57 (br. s., 14 H) 1.73 (d,  $J=1.26$  Hz, 2 H) 1.83 (br. s., 1 H) 2.17 (br. s., 1 H) 2.69 - 2.78 (m, 4 H) 3.14 (br. s., 2 H) 3.27 (s, 3 H) 3.74 (br. s., 2 H) 4.18 (t,  $J=7.20$  Hz, 1 H) 7.70 - 7.81 (m, 5 H) 7.93 (d,  $J=8.59$  Hz, 1 H) 8.47 (s, 1 H) 8.56 (br. s., 1 H) 10.32 (br. s., 1 H) 12.93 (s, 1 H).

4-35 3-[(2-[(R)-3-Cyclopentyl-2-[4-(4-methyl-piperazine-1-sulfonyl)-phenyl]-propionylamino]-benzothiazole-6-carbonyl)-amino]-propionic acid: MS  $M+1$  629,  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ )  $\delta$  ppm 1.15 (br. s., 2 H) 1.45 (br. s., 2 H) 1.57 (br. s., 3 H) 1.73 (br. s., 2 H) 2.17 (br. s., 1 H) 2.62 (br. s., 2 H) 2.72 (br. s., 4 H) 3.14 (br. s., 2 H) 3.27 (s, 3 H) 3.45 (dd,  $J=10.23, 4.67$  Hz, 6 H) 3.54 (br. s., 4 H) 3.74 (br. s., 2 H) 4.18 (s, 1 H) 7.71 - 7.82 (m, 5 H) 7.92 (s, 1 H) 8.47 (s, 1 H) 8.57 (br. s., 1 H) 10.33 (br. s., 1 H) 12.93 (s, 2 H).

4-36 3-Cyclopentyl-2-[4-(4-methyl-piperazine-1-sulfonyl)-phenyl]-N-(6-trifluoromethoxy-benzothiazol-2-yl)-propionamide: MS  $M+1$  598,  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ )  $\delta$  ppm 1.16 (br. s., 1 H) 1.10 (d,  $J=6.82$  Hz, 1 H) 1.45 (br. s., 2 H) 1.57 (br. s., 2 H) 1.62 (br. s., 2 H) 1.72 (br. s., 1 H) 1.81 (br. s., 2 H) 2.19 (d,  $J=5.31$  Hz, 1 H) 2.72 (br. s., 4 H) 3.14 (br. s., 2 H) 3.37 - 3.49 (m, 2 H) 3.78 (br. s., 26 H) 4.19 (t,  $J=7.07$  Hz, 1 H) 7.43 (d,  $J=8.34$  Hz, 1 H) 7.71 - 7.76 (m, 2 H) 7.77 - 7.85 (m, 1 H) 7.79 (d,  $J=8.34$  Hz, 1 H) 8.12 (br. s., 1 H) 10.61 (br. s., 1 H) 12.92 (br. s., 1 H).

4-37 N-(5-Chloro-thiazolo[5,4-b]pyridin-2-yl)-3-cyclopentyl-2-[4-(4-methyl-piperazine-1-sulfonyl)-phenyl]-propionamide: MS  $M+1$  548,  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ )  $\delta$  ppm 0.82 - 0.89 (m, 1 H) 1.14 (t,  $J=7.20$  Hz, 2 H) 1.43 (br. s., 2 H) 1.56 (br. s., 3 H) 1.70 (br. s., 2 H) 1.75 - 1.85 (m, 1 H) 2.57 (br. s., 2 H) 2.73 (br. s., 3 H) 3.13 (br. s., 2 H) 3.40 (br. s., 6 H) 3.71 - 3.82 (m, 2 H) 4.12 - 4.19 (m, 1 H) 7.58 (d, 1 H) 7.55 (s, 1 H) 7.69 - 7.80 (m, 3 H) 8.16 (d,  $J=8.59$  Hz, 1 H) 9.85 (br. s., 1 H) 13.03 (s, 1 H).

4-38 (2-{3-Cyclopentyl-2-[4-(4-methyl-piperazine-1-sulfonyl)-phenyl]-propionylamino}-thiazolo[5,4-b]pyridin-5-yloxy)-acetic acid: MS M+1 588, <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ ppm 1.09 (br. s., 2 H) 1.40 (d, *J*=6.32 Hz, 2 H) 1.53 (d, *J*=6.57 Hz, 3 H) 1.63 - 1.72 (m, 3 H) 2.04 - 2.13 (m, 5 H) 2.32 (d, *J*=4.04 Hz, 5 H) 2.86 (br. s., 4 H) 3.58 - 3.64 (m, 1 H) 4.25 (s, 2 H) 6.47 (d, *J*=8.59 Hz, 1 H) 7.45 (d, *J*=8.59 Hz, 1 H) 7.57 - 7.65 (m, 4 H).

4-39 3-Cyclopentyl-N-(5-fluoro-thiazolo[5,4-b]pyridin-2-yl)-2-[4-(4-methyl-piperazine-1-sulfonyl)-phenyl]-propionamide: MS M+1 532, <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ ppm 1.14 (d, *J*=7.07 Hz, 2 H) 1.43 (d, *J*=7.07 Hz, 2 H) 1.56 (d, *J*=4.29 Hz, 3 H) 1.72 (br. s., 2 H) 1.75 - 1.86 (m, 1 H) 2.18 (br. s., 1 H) 2.60 (br. s., 2 H) 2.71 (br. s., 2 H) 3.12 (br. s., 2 H) 3.32 (br. s., 4 H) 3.41 (br. s., 1 H) 3.75 (br. s., 1 H) 4.17 (br. s., 1 H) 7.27 (d, *J*=8.59 Hz, 1 H) 7.69 - 7.81 (m, 4 H) 8.26 - 8.35 (m, 1 H) 10.22 (br. s., 1 H) 12.97 (s, 1 H).

4-40 3-Cyclopentyl-2-[4-(4-methyl-piperazine-1-sulfonyl)-phenyl]-N-(5-vinyl-thiazolo[5,4-b]pyridin-2-yl)-propionamide: MS M+1 540, <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ ppm 1.25 (d, *J*=7.07 Hz, 3 H) 1.55 (d, *J*=7.07 Hz, 3 H) 1.67 (d, *J*=7.07 Hz, 4 H) 1.82 (d, *J*=10.61 Hz, 2 H) 1.94 (d, *J*=6.57 Hz, 1 H) 2.27 (s, 1 H) 2.67 (br. s., 2 H) 2.84 (d, *J*=3.79 Hz, 4 H) 3.22 (br. s., 2 H) 3.53 (br. s., 2 H) 3.85 (br. s., 2 H) 4.28 (t, *J*=7.71 Hz, 1 H) 5.60 (dd, *J*=10.86, 1.26 Hz, 1 H) 6.35 (dd, *J*=17.43, 1.26 Hz, 1 H) 7.00 (dd, *J*=17.56, 10.74 Hz, 1 H) 7.74 (d, *J*=8.34 Hz, 1 H) 7.82 - 7.86 (m, 2 H) 7.87 - 7.93 (m, 2 H) 8.17 (d, *J*=8.34 Hz, 1 H) 10.08 (br. s., 1 H) 13.01 (s, 1 H).

4-41 3-Cyclopentyl-N-(5-ethyl-thiazolo[5,4-b]pyridin-2-yl)-2-[4-(4-methyl-piperazine-1-sulfonyl)-phenyl]-propionamide: MS M+1 542, <sup>1</sup>H NMR (400 MHz, DMSO-*D*<sub>6</sub>) δ ppm 1.10 - 1.21 (m, 2 H) 1.26 (t, *J*=7.58 Hz, 3 H) 1.45 (dd, *J*=7.20, 4.67 Hz, 2 H) 1.52 - 1.64 (m, 3 H) 1.73 (s, 2 H) 1.82 (ddd, *J*=13.58, 7.07, 6.88 Hz, 1 H) 2.13 - 2.22 (m, 1 H) 2.67 (s, 2 H) 2.72 (d, *J*=4.04 Hz, 3 H) 2.85 (q, *J*=7.66 Hz, 2 H) 3.14 (s, 2 H) 3.43 (d, *J*=12.38 Hz, 2 H) 3.74 (s, 2 H) 4.18 (t, *J*=7.58 Hz, 1 H) 7.37 (d, *J*=8.34 Hz, 1 H) 7.70 - 7.76 (m, 2 H) 7.76 - 7.81 (m, 2 H) 8.01 (d, *J*=8.34 Hz, 1 H).

4-42 3-Cyclopentyl-2-[4-(4-methyl-piperazine-1-sulfonyl)-phenyl]-N-(5-morpholin-4-yl-thiazolo[5,4-b]pyridin-2-yl)-propionamide: MS M+1 599, <sup>1</sup>H NMR (400 MHz, DMSO) δ 1.14 (m, 2H) 1.43 (d, *J* = 4.80Hz, 2H) 1.57 (d, *J* = 8.34Hz, 3H) 1.72 (d, *J* = 5.05Hz, 2H) 1.75-1.83 (m, 1H) 2.10 (s, 3H) 2.16 (m, 1H) 2.33 (d, *J* = 4.04Hz, 4H) 2.87 (s, 4H) 3.41-3.49 (m, 4H)

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3.67-3.74 (m, 4H) 4.07 (t,  $J = 7.58\text{Hz}$ , 1H) 6.97 (d,  $J = 9.09\text{Hz}$ , 1H) 7.64-7.69 (m, 2H) 7.69-7.75 (m, 2H) 7.87 (d,  $J = 8.84\text{Hz}$ , 1H).

4-43 3-Cyclopentyl-2-[4-(4-methyl-piperazine-1-sulfonyl)-phenyl]-N-(5-pyridin-3-yl-thiazolo[5,4-b]pyridin-2-yl)-propionamide: MS  $M+1$  591,  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ )  $\delta$  ppm 1.17 (t,  $J=7.20\text{ Hz}$ , 1 H) 1.14 (d,  $J=8.34\text{ Hz}$ , 1 H) 1.45 (dd,  $J=7.33, 4.80\text{ Hz}$ , 2 H) 1.57 (d,  $J=2.27\text{ Hz}$ , 2 H) 1.62 (d,  $J=7.58\text{ Hz}$ , 1 H) 1.72 (br. s., 2 H) 1.85 (d,  $J=6.82\text{ Hz}$ , 1 H) 2.10 (s, 3 H) 2.18 (d,  $J=13.14\text{ Hz}$ , 1 H) 2.33 (d,  $J=3.54\text{ Hz}$ , 4 H) 2.88 (br. s., 4 H) 4.14 (t,  $J=7.45\text{ Hz}$ , 1 H) 7.53 (dd,  $J=7.96, 4.67\text{ Hz}$ , 1 H) 7.67 - 7.76 (m, 4 H) 8.14 - 8.23 (m, 3 H) 8.48 (ddd,  $J=8.34, 2.02, 1.77\text{ Hz}$ , 1 H) 8.63 (dd,  $J=4.80, 1.77\text{ Hz}$ , 1 H) 9.30 (d,  $J=1.52\text{ Hz}$ , 1 H) 12.92 (s, 1 H).

4-44 3-Cyclopentyl-2-[4-(4-methyl-piperazine-1-sulfonyl)-phenyl]-N-(5-phenyl-thiazolo[5,4-b]pyridin-2-yl)-propionamide: MS  $M+1$  590,  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ )  $\delta$  ppm 1.20 (d,  $J=8.08\text{ Hz}$ , 2 H) 1.50 (d,  $J=7.33\text{ Hz}$ , 2 H) 1.63 (d,  $J=4.80\text{ Hz}$ , 1 H) 1.68 (s, 2 H) 1.80 (s, 1 H) 1.84 - 1.94 (m, 1 H) 2.25 (m, 1 H) 2.81 (s, 3 H) 3.20 (br. s., 2 H) 3.49 (br. s., 52 H) 3.80 (br. s., 2 H) 4.22 (t,  $J=7.58\text{ Hz}$ , 1 H) 7.46 - 7.53 (m, 1 H) 7.53 - 7.58 (m, 2 H) 7.77 - 7.82 (m, 2 H) 7.82 - 7.87 (m, 2 H) 8.12 (d,  $J=8.59\text{ Hz}$ , 1 H) 8.15 - 8.19 (m, 2 H) 8.22 (d,  $J=8.59\text{ Hz}$ , 1 H) 9.39 (br. s., 1 H) 12.96 (s, 1 H).  $\text{EC}_{50}$  in primary enzyme assay  $0.26\mu\text{M}$

4-45 3-Cyclopentyl-2-[4-(4-methyl-piperazine-1-sulfonyl)-3-trifluoromethyl-phenyl]-N-(5-pyridin-4-yl-thiazolo[5,4-b]pyridin-2-yl)-propionamide: MS  $M+1$  659,  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ )  $\delta$  ppm 1.17 (ddd,  $J=19.64, 11.68, 8.08\text{ Hz}$ , 2 H) 1.46 (dd,  $J=7.07, 4.55\text{ Hz}$ , 2 H) 1.53 - 1.64 (m, 3 H) 1.68 (d,  $J=16.42\text{ Hz}$ , 2 H) 1.88 (ddd,  $J=13.52, 6.95, 6.82\text{ Hz}$ , 1 H) 2.24 (ddd,  $J=13.33, 7.83, 7.64\text{ Hz}$ , 1 H) 2.76 (s, 3 H) 3.11 (br. s., 1 H) 3.22 (d,  $J=6.32\text{ Hz}$ , 2 H) 3.39 - 3.50 (m, 2 H) 3.84 (d,  $J=2.53\text{ Hz}$ , 3 H) 4.35 (t,  $J=7.58\text{ Hz}$ , 1 H) 7.99 (dd,  $J=8.34, 1.26\text{ Hz}$ , 1 H) 8.14 (d,  $J=8.34\text{ Hz}$ , 1 H) 8.10 (d,  $J=1.26\text{ Hz}$ , 1 H) 8.33 (d,  $J=8.59\text{ Hz}$ , 1 H) 8.39 - 8.46 (m, 1 H) 8.53 (d,  $J=6.32\text{ Hz}$ , 2 H) 8.90 (d,  $J=6.32\text{ Hz}$ , 2 H) 13.21 (s, 1 H).

4-46 3-Cyclopentyl-N-[5-(2-methoxy-ethoxy)-thiazolo[5,4-b]pyridin-2-yl]-2-[4-(4-methyl-piperazine-1-sulfonyl)-phenyl]-propionamide: MS  $M+1$  588,  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ )  $\delta$  ppm 0.82 - 0.89 (m, 1 H) 1.14 (br. s., 2 H) 1.25 (d,  $J=19.45\text{ Hz}$ , 2 H) 1.42 (br. s., 2 H) 1.56 (br. s., 3 H) 1.71 (br. s., 2 H) 1.81 (s, 1 H) 2.73 (br. s., 2 H) 3.12 (br. s., 2 H) 3.29 (s, 3 H) 3.39 (br. s., 6 H) 3.61 - 3.71 (m, 2 H) 3.77 (br. s., 1 H) 4.12 (br. s., 1 H) 4.40 (dd,  $J=5.18,$

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3.66 Hz, 2 H) 6.91 (d,  $J=8.59$  Hz, 1 H) 7.67 - 7.74 (m, 2 H) 7.76 - 7.80 (m, 2 H) 8.02 (d,  $J=8.84$  Hz, 1 H) 9.60 (br. s., 1 H) 12.70 (br. s., 1 H).

4-47 4-(2-{3-Cyclopentyl-2-[4-(4-methyl-piperazine-1-sulfonyl)-phenyl]-propionylamino}-thiazolo[5,4-b]pyridin-5-yloxy)-butyric acid: MS M+1 616,  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  ppm 1.09 (br. s., 2 H) 1.34 - 1.45 (m, 2 H) 1.54 (br. s., 2 H) 1.60 (s, 1 H) 1.63 - 1.73 (m, 3 H) 1.82 (q,  $J=7.07$  Hz, 2 H) 1.97 (br. s., 2 H) 2.03 - 2.13 (m, 5 H) 2.31 (t,  $J=4.42$  Hz, 5 H) 2.85 (br. s., 4 H) 3.65 (s, 1 H) 4.13 (t,  $J=6.82$  Hz, 2 H) 6.54 (d,  $J=8.59$  Hz, 1 H) 7.52 (d,  $J=8.59$  Hz, 1 H) 7.58 - 7.64 (m, 4 H).

4-48 3-Cyclopentyl-N-{5-[(2-methoxy-ethyl)-methyl-amino]-thiazolo[5,4-b]pyridin-2-yl}-2-[4-(4-methyl-piperazine-1-sulfonyl)-phenyl]-propionamide: MS M+1 601,  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  ppm -1.13 (ddd,  $J=16.48, 11.68, 8.21$  Hz, 2 H) 1.39 - 1.49 (m, 1 H) 1.44 (dd,  $J=7.20, 4.67$  Hz, 1 H) 1.52 - 1.63 (m,  $J=15.09, 7.83, 7.61, 7.61$  Hz, 3 H) 1.76 (td,  $J=13.58, 7.20$  Hz, 2 H) 1.70 (d,  $J=3.54$  Hz, 1 H) 2.09 - 2.19 (m, 4 H) 2.32 (t,  $J=4.55$  Hz, 4 H) 2.87 (br. s., 4 H) 3.06 (s, 3 H) 3.24 (s, 3 H) 3.51 (d,  $J=11.37$  Hz, 1 H) 3.51 (s, 1 H) 3.71 (t,  $J=5.68$  Hz, 2 H) 4.07 (t,  $J=7.45$  Hz, 1 H) 6.76 (d,  $J=9.09$  Hz, 1 H) 7.64 - 7.69 (m, 2 H) 7.70 - 7.75 (m, 2 H) 7.80 (d,  $J=9.09$  Hz, 1 H) 12.40 (br. s., 1 H).

4-49 3-(2-{(R)-3-Cyclopentyl-2-[4-(4-methyl-piperazine-1-sulfonyl)-phenyl]-propionylamino}-thiazolo[5,4-b]pyridin-5-yloxy)-2,2-dimethyl-propionic acid: MS M+1 630,  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  ppm 1.05 - 1.15 (m, 7 H) 1.36 - 1.47 (m, 2 H) 1.51 - 1.63 (m, 3 H) 1.69 (d,  $J=6.06$  Hz, 3 H) 2.07 - 2.15 (m, 4 H) 2.32 (t,  $J=4.55$  Hz, 4 H) 2.86 (br. s., 4 H) 3.31 (br. s., 3 H) 3.74 (br. s., 1 H) 4.14 (s, 2 H) 6.58 (d,  $J=8.34$  Hz, 1 H) 7.57 - 7.66 (m, 5 H).

4-50 3-Cyclopentyl-2-[4-(4-methyl-piperazine-1-sulfonyl)-phenyl]-N-[5-(4-methyl-piperazin-1-yl)-thiazolo[5,4-b]pyridin-2-yl]-propionamide: MS M+1 613,  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  ppm 1.14 (dd,  $J=11.87, 7.58$  Hz, 1 H) 1.10 (br. s., 1 H) 1.46 (br. s., 1 H) 1.44 (d,  $J=4.80$  Hz, 1 H) 1.52 - 1.63 (m, 2 H) 1.57 (d,  $J=4.04$  Hz, 1 H) 1.69 - 1.81 (m, 2 H) 2.16 (ddd,  $J=13.20, 7.83, 7.52$  Hz, 1 H) 2.71 (d,  $J=3.54$  Hz, 5 H) 2.78 (d,  $J=4.55$  Hz, 3 H) 3.07 (d,  $J=11.12$  Hz, 4 H) 3.26 - 3.37 (m, 2 H) 3.38 - 3.50 (m, 1 H) 3.74 (br. s., 2 H) 4.17 (t,  $J=7.45$  Hz, 1 H) 4.39 (d,  $J=13.39$  Hz, 2 H) 7.09 (d,  $J=9.09$  Hz, 1 H) 7.68 - 7.74 (m, 2 H) 7.74 - 7.81 (m, 2 H) 7.95 (d,  $J=8.84$  Hz, 1 H) 10.91 (br. s., 1 H) 11.10 (br. s., 1 H) 12.67 (s, 1 H)

4-51 3-Cyclopentyl-2-[4-(4-methyl-piperazine-1-sulfonyl)-phenyl]-N-(5-piperidin-1-yl-thiazolo[5,4-b]pyridin-2-yl)-propionamide: MS M+1 597, <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ ppm 1.09 - 1.19 (m, 2 H) 1.45 (dd, *J*=7.20, 4.42 Hz, 2 H) 1.53 - 1.63 (m, 3 H) 1.57 (dd, *J*=6.69, 4.17 Hz, 7 H) 1.77 (dd, *J*=13.52, 6.95 Hz, 2 H) 2.16 (ddd, *J*=13.07, 7.83, 7.64 Hz, 1 H) 2.63 (t, *J*=12.13 Hz, 2 H) 2.73 (d, *J*=3.79 Hz, 3 H) 3.11 (br. s., 2 H) 3.43 (d, *J*=11.62 Hz, 2 H) 3.54 (d, *J*=5.56 Hz, 3 H) 3.74 (br. s., 2 H) 4.13 (t, *J*=7.58 Hz, 1 H) 6.96 (d, *J*=9.09 Hz, 1 H) 7.69 - 7.74 (m, 2 H) 7.77 - 7.83 (m, 2 H) 7.80 (d, *J*=4.29 Hz, 1 H) 10.37 (br. s., 1 H) 12.53 (s, 1 H).

4-52 2-[(R)-3-Cyclopentyl-2-[4-(4-methyl-piperazine-1-sulfonyl)-phenyl]-propionylamino]-thiazolo[5,4-b]pyridine-5-carboxylic acid (2-methoxy-ethyl)-methyl-amide: MS M+1 629, <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ ppm 1.15 (br. s., 2 H) 1.40 - 1.52 (m, 2 H) 1.57 (br. s., 3 H) 1.72 (br. s., 2 H) 2.17 (s, 1 H) 2.57 (br. s., 2 H) 2.73 (br. s., 2 H) 3.01 (d, *J*=15.16 Hz, 3 H) 3.11 (s, 3 H) 3.31 (d, *J*=7.33 Hz, 9 H) 3.45 (d, *J*=5.81 Hz, 3 H) 3.59 (d, *J*=5.31 Hz, 1 H) 3.63 (br. s., 1 H) 3.76 (br. s., 1 H) 4.18 (t, *J*=7.96 Hz, 1 H) 7.64 (d, *J*=8.34 Hz, 1 H) 7.70 - 7.81 (m, 3 H) 8.18 (d, *J*=8.34 Hz, 1 H) 9.88 (br. s., 1 H) 13.03 (s, 1 H). EC<sub>50</sub> in primary enzyme assay 2.1 μM

4-53 3-Cyclopentyl-N-[5-((2R,6S)-2,6-dimethyl-morpholin-4-yl)-thiazolo[5,4-b]pyridin-2-yl]-2-[4-(4-methyl-piperazine-1-sulfonyl)-phenyl]-propionamide: MS M+1 627, <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ ppm 1.11 - 1.21 (m, 2 H) 1.17 (d, *J*=6.06 Hz, 6 H) 1.45 (dd, *J*=7.33, 4.55 Hz, 2 H) 1.52 - 1.63 (m, 2 H) 1.58 (d, *J*=8.08 Hz, 2 H) 1.72 (br. s., 2 H) 1.78 (dd, *J*=13.39, 7.07 Hz, 1 H) 2.16 (ddd, *J*=13.33, 7.83, 7.64 Hz, 1 H) 2.43 (dd, *J*=12.51, 10.74 Hz, 3 H) 2.56 - 2.64 (m, 2 H) 2.73 (d, *J*=3.79 Hz, 3 H) 3.12 (br. s., 2 H) 3.39 - 3.47 (m, 2 H) 3.62 (ddd, *J*=10.42, 6.38, 2.40 Hz, 2 H) 3.76 (d, *J*=12.38 Hz, 2 H) 4.13 (d, *J*=13.64 Hz, 2 H) 4.12 (d, *J*=4.55 Hz, 1 H) 6.99 (d, *J*=9.09 Hz, 1 H) 7.69 - 7.74 (m, 2 H) 7.79 (d, *J*=6.32 Hz, 2 H) 7.87 (d, *J*=8.84 Hz, 1 H) 10.22 (br. s., 1 H) 12.57 (s, 1 H).

4-54 3-Cyclopentyl-2-[4-(4-methyl-piperazine-1-sulfonyl)-phenyl]-N-[5-(2-methyl-pyridin-4-yl)-thiazolo[5,4-b]pyridin-2-yl]-propionamide: MS M+1 605, <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ ppm 1.11 - 1.24 (m, 2 H) 1.46 (dd, *J*=7.33, 4.80 Hz, 2 H) 1.59 (ddd, *J*=15.09, 7.39, 7.07 Hz, 3 H) 1.73 (d, *J*=11.62 Hz, 2 H) 1.85 (ddd, *J*=13.58, 7.07, 6.88 Hz, 1 H) 2.19 (ddd, *J*=13.20, 7.83, 7.52 Hz, 1 H) 2.67 (d, *J*=1.77 Hz, 1 H) 2.71 (s, 3 H) 2.80 (s, 3 H) 3.14 (br. s., 2 H) 3.37 - 3.48 (m, 2 H) 3.70 - 3.82 (m, 2 H) 3.71 (d, *J*=1.52 Hz, 1 H) 4.25 (t, *J*=7.58 Hz, 1 H) 7.72 -



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7.82 (m, 4 H) 8.35 (d,  $J=8.34$  Hz, 1 H) 8.46 (d,  $J=8.59$  Hz, 2 H) 8.59 (s, 1 H) 8.82 (d,  $J=6.06$  Hz, 1 H) 10.71 (br. s., 1 H) 13.23 (s, 1 H).

4-55 3-Cyclopentyl-N-(5-ethynyl-thiazolo[5,4-b]pyridin-2-yl)-2-[4-(4-methyl-piperazine-1-sulfonyl)-phenyl]-propionamide: MS  $M+1$  538,  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  ppm 1.15 (t,  $J=7.07$  Hz, 2 H) 1.45 (dd,  $J=7.33, 4.55$  Hz, 2 H) 1.53 - 1.64 (m, 2 H) 1.59 (d,  $J=7.07$  Hz, 2 H) 1.72 (d,  $J=5.05$  Hz, 2 H) 1.70 (br. s., 1 H) 1.83 (ddd,  $J=13.39, 7.07, 6.82$  Hz, 1 H) 2.19 (dt,  $J=13.45, 7.67$  Hz, 1 H) 2.76 (s, 3 H) 3.15 (br. s., 2 H) 3.44 (br. s., 2 H) 3.76 (br. s., 2 H) 4.16 (t,  $J=7.71$  Hz, 1 H) 4.42 (s, 1 H) 7.65 (d,  $J=8.34$  Hz, 1 H) 7.71 - 7.75 (m, 2 H) 7.77 - 7.81 (m, 2 H) 8.10 (d,  $J=8.34$  Hz, 1 H) 13.01 (s, 1 H).

4-56 3-Cyclopentyl-2-[4-(4-methyl-piperazine-1-sulfonyl)-phenyl]-N-(5-pyrimidin-5-yl-thiazolo[5,4-b]pyridin-2-yl)-propionamide: MS  $M+1$  593,  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  ppm 1.17 (d,  $J=7.83$  Hz, 2 H) 1.46 (dd,  $J=7.20, 4.67$  Hz, 2 H) 1.53 - 1.65 (m, 3 H) 1.76 (br. s., 1 H) 1.73 (d,  $J=11.62$  Hz, 2 H) 1.84 (ddd,  $J=13.52, 6.95, 6.82$  Hz, 1 H) 2.19 (ddd,  $J=13.33, 7.83, 7.64$  Hz, 1 H) 2.57 - 2.68 (m, 1 H) 2.67 (d,  $J=1.77$  Hz, 1 H) 2.73 (d,  $J=4.29$  Hz, 3 H) 3.14 (br. s., 2 H) 3.42 (br. s., 2 H) 3.77 (d,  $J=12.88$  Hz, 2 H) 7.72 - 7.82 (m, 4 H) 8.23 - 8.29 (m, 2 H) 9.25 (s, 1 H) 9.49 (s, 2 H) 13.05 (s, 1 H).

4-57 2-{3-Cyclopentyl-2-[4-(4-methyl-piperazine-1-sulfonyl)-phenyl]-propionylamino}-thiazolo[5,4-b]pyridine-5-carboxylic acid (2-methoxy-ethyl)-amide: MS  $M+1$  615,  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  ppm 1.15 (br. s., 2 H) 1.43 (br. s., 2 H) 1.52 - 1.63 (m, 4 H) 1.71 (br. s., 2 H) 1.83 (d,  $J=13.39$  Hz, 1 H) 2.17 (s, 1 H) 2.75 (br. s., 3 H) 3.14 (br. s., 2 H) 3.40 - 3.51 (m, 6 H) 3.61 (s, 3 H) 3.75 (br. s., 3 H) 4.17 (s, 1 H) 7.71 - 7.81 (m, 4 H) 8.13 (d,  $J=8.59$  Hz, 1 H) 8.23 (d,  $J=8.34$  Hz, 1 H) 8.76 (br. s., 1 H) 9.37 (br. s., 1 H) 13.08 (s, 1 H).

4-58 2-{3-Cyclopentyl-2-[4-(4-methyl-piperazine-1-sulfonyl)-phenyl]-propionylamino}-thiazolo[5,4-b]pyridine-5-carboxylic acid dimethylamide: MS  $M+1$  585,  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  ppm 1.15 (br. s., 2 H) 1.44 (br. s., 2 H) 1.57 (br. s., 3 H) 1.72 (br. s., 2 H) 1.81 (br. s., 1 H) 2.18 (br. s., 1 H) 2.74 (br. s., 3 H) 2.95 (s, 2 H) 2.98 - 3.06 (m, 3 H) 3.12 (br. s., 2 H) 3.44 (br. s., 1 H) 3.60 (br. s., 4 H) 3.74 (br. s., 2 H) 4.15 (br. s., 1 H) 7.64 (d,  $J=8.34$  Hz, 1 H) 7.70 - 7.82 (m, 4 H) 8.18 (d,  $J=8.34$  Hz, 1 H) 9.32 (br. s., 1 H) 12.99 (s, 1 H).

4-59 3-Cyclopentyl-N-[5-(2-hydroxy-ethoxy)-thiazolo[5,4-b]pyridin-2-yl]-2-[4-(4-methyl-piperazine-1-sulfonyl)-phenyl]-propionamide: MS M+1 574, <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ ppm 1.14 (br. s., 2 H) 1.43 (d, *J*=6.82 Hz, 2 H) 1.51 - 1.63 (m, 3 H) 1.73 (d, *J*=10.11 Hz, 2 H) 2.17 (d, *J*=6.06 Hz, 1 H) 2.73 (d, *J*=13.14 Hz, 5 H) 2.88 (s, 2 H) 3.14 (br. s., 2 H) 3.43 (br. s., 2 H) 3.71 (t, *J*=5.05 Hz, 4 H) 4.11 (t, *J*=7.33 Hz, 1 H) 4.29 (t, *J*=4.93 Hz, 2 H) 6.89 (d, *J*=8.84 Hz, 1 H) 7.69 - 7.81 (m, 4 H) 8.01 (d, *J*=8.84 Hz, 1 H) 9.46 (br. s., 1 H) 12.69 (s, 1 H).

4-60 3-Cyclopentyl-2-[4-(4-methyl-piperazine-1-sulfonyl)-phenyl]-N-(5-pyridin-4-yl-thiazolo[5,4-b]pyridin-2-yl)-propionamide: MS M+1 591, <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ ppm 1.27 (t, *J*=7.20 Hz, 3 H) 1.54 (br. s., 1 H) 1.53 (d, *J*=5.05 Hz, 1 H) 1.63 - 1.74 (m, 2 H) 1.66 (d, *J*=2.27 Hz, 2 H) 1.80 (d, *J*=3.03 Hz, 2 H) 1.89 - 1.97 (m, 1 H) 2.19 (s, 3 H) 2.23 - 2.33 (m, 1 H) 2.41 (t, *J*=4.42 Hz, 4 H) 2.97 (br. s., 4 H) 4.22 (t, 1 H) 7.74 - 7.84 (m, 4 H) 8.18 (d, *J*=6.06 Hz, 1 H) 8.18 (d, *J*=3.03 Hz, 1 H) 8.29 (s, 2 H) 8.79 (d, *J*=6.06 Hz, 1 H) 8.79 (d, *J*=3.03 Hz, 1 H) 13.06 (br. s., 1 H).

4-61 3-Cyclopentyl-2-[4-(4-methyl-piperazine-1-sulfonyl)-phenyl]-N-[5-(morpholine-4-carbonyl)-thiazolo[5,4-b]pyridin-2-yl]-propionamide: MS M+1 627, <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ ppm 0.90 - 1.00 (m, 1 H) 0.94 (d, *J*=7.58 Hz, 1 H) 1.25 (br. s., 1 H) 1.23 (d, *J*=4.80 Hz, 1 H) 1.32 - 1.44 (m, 1 H) 1.38 (d, *J*=13.39 Hz, 2 H) 1.51 (d, *J*=11.62 Hz, 2 H) 1.63 (d, *J*=6.82 Hz, 1 H) 1.93 - 2.02 (m, 1 H) 1.98 (d, *J*=13.39 Hz, 1 H) 2.32 (br. s., 2 H) 2.53 (br. s., 3 H) 2.92 (br. s., 2 H) 3.23 - 3.30 (m, 4 H) 3.35 (d, *J*=5.81 Hz, 2 H) 3.41 - 3.51 (m, 4 H) 3.98 (t, *J*=7.58 Hz, 1 H) 7.47 - 7.55 (m, 1 H) 7.49 (d, *J*=8.34 Hz, 2 H) 7.56 - 7.62 (m, 2 H) 8.00 (d, *J*=8.34 Hz, 1 H) 9.73 (br. s., 1 H) 12.83 (s, 1 H).

4-62 3-Cyclopentyl-N-(5-isopropoxy-thiazolo[5,4-b]pyridin-2-yl)-2-[4-(4-methyl-piperazine-1-sulfonyl)-phenyl]-propionamide: MS M+1 572, <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ ppm 0.79 - 0.89 (m, 1 H) 1.14 (br. s., 2 H) 1.22 - 1.32 (m, 6 H) 1.44 (dd, *J*=7.07, 4.55 Hz, 2 H) 1.51 - 1.63 (m, 3 H) 1.71 (br. s., 1 H) 1.74 - 1.83 (m, 1 H) 2.11 - 2.21 (m, 1 H) 2.72 (br. s., 2 H) 3.11 (br. s., 2 H) 3.41 (br. s., 3 H) 3.46 (br. s., 2 H) 3.73 (br. s., 2 H) 4.09 - 4.17 (m, 1 H) 5.20 - 5.29 (m, *J*=6.19, 6.19, 6.19, 6.19 Hz, 1 H) 6.82 (d, *J*=8.84 Hz, 1 H) 7.66 - 7.73 (m, 2 H) 7.75 - 7.80 (m, 2 H) 7.99 (d, *J*=8.84 Hz, 1 H) 10.02 (br. s., 1 H) 12.69 (s, 1 H).

4-63 N-(5-Benzyl-thiazolo[5,4-b]pyridin-2-yl)-3-cyclopentyl-2-[4-(4-methyl-piperazine-1-sulfonyl)-phenyl]-propionamide: MS M+1 604, <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ ppm 1.09 -

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1.20 (m, 1 H) 1.15 (t,  $J=7.20$  Hz, 2 H) 1.44 (ddd,  $J=11.81, 7.14, 6.82$  Hz, 3 H) 1.52 - 1.61 (m, 1 H) 1.57 (d,  $J=4.29$  Hz, 2 H) 1.66 - 1.76 (m, 1 H) 1.71 (d,  $J=9.35$  Hz, 2 H) 1.80 (dd,  $J=13.52, 6.95$  Hz, 1 H) 2.17 (ddd,  $J=13.26, 7.96, 7.83$  Hz, 1 H) 2.62 (t,  $J=12.25$  Hz, 1 H) 2.72 (d,  $J=3.79$  Hz, 2 H) 3.14 (br. s., 2 H) 3.39 - 3.48 (m, 1 H) 3.42 (d,  $J=12.13$  Hz, 1 H) 3.70 - 3.81 (m, 1 H) 3.76 (d,  $J=12.88$  Hz, 1 H) 4.18 (s, 2 H) 7.20 (dd,  $J=9.22, 4.42$  Hz, 1 H) 7.29 (d,  $J=1.26$  Hz, 1 H) 7.26 - 7.31 (m, 2 H) 7.37 (d,  $J=8.34$  Hz, 1 H) 7.70 - 7.75 (m, 2 H) 7.75 - 7.81 (m, 2 H) 8.02 (d,  $J=8.34$  Hz, 1 H) 10.34 (br. s., 1 H) 12.84 (s, 1 H).

4-64 N-(5-Amino-thiazolo[5,4-b]pyridin-2-yl)-3-cyclopentyl-2-[4-(4-methyl-piperazine-1-sulfonyl)-phenyl]-propionamide: MS  $M+1$  529,  $^1\text{H}$  NMR (400 MHz, CHLOROFORM- $D$ )  $\delta$  ppm 1.13 (s, 2 H) 1.49 (s, 2 H) 1.62 (s, 3 H) 1.74 (s, 2 H) 1.91 (s, 1 H) 2.26 (s, 4 H) 2.48 (s, 4 H) 3.06 (s, 4 H) 3.66 (s, 1 H) 4.54 (s, 2 H) 6.57 (d,  $J=8.72$  Hz, 1 H) 7.49 - 7.54 (m, 2 H) 7.71 (d,  $J=8.72$  Hz, 1 H) 7.74 (d,  $J=8.46$  Hz, 2 H).

4-65 3-Cyclopentyl-N-[5-(2-methoxy-ethylamino)-thiazolo[5,4-b]pyridin-2-yl]-2-[4-(4-methyl-piperazine-1-sulfonyl)-phenyl]-propionamide: MS  $M+1$  587,  $^1\text{H}$  NMR (400 MHz, DMSO- $D_6$ )  $\delta$  ppm 1.24 (s, 2 H) 1.49 - 1.58 (m, 2 H) 1.66 (s, 3 H) 1.86 (d,  $J=6.82$  Hz, 3 H) 2.25 (d,  $J=12.51$  Hz, 1 H) 2.53 (s, 2 H) 2.85 (s, 3 H) 3.26 (d,  $J=13.89$  Hz, 2 H) 3.36 (s, 3 H) 3.48 - 3.59 (m, 5 H) 3.84 (s, 2 H) 4.15 - 4.22 (m, 1 H) 6.72 (d,  $J=8.97$  Hz, 1 H) 7.76 - 7.84 (m, 3 H) 7.85 - 7.90 (m, 2 H).

4-66 2-[3-Chloro-4-(4-methyl-piperazine-1-sulfonyl)-phenyl]-N-(5-chloro-thiazolo[5,4-b]pyridin-2-yl)-3-cyclopentyl-propionamide: MS  $M+1$  582,  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  ppm 0.82 - 0.91 (m, 1 H) 1.15 (br. s., 2 H) 1.23 (br. s., 2 H) 1.44 (br. s., 2 H) 1.58 (br. s., 2 H) 1.63 (br. s., 1 H) 1.72 (br. s., 2 H) 1.77 - 1.88 (m, 1 H) 2.15 (br. s., 1 H) 2.78 (br. s., 2 H) 3.09 (br. s., 4 H) 3.45 (br. s., 1 H) 3.85 (br. s., 1 H) 4.14 (br. s., 1 H) 7.55 - 7.65 (m, 2 H) 7.76 (s, 1 H) 8.00 (d,  $J=8.34$  Hz, 1 H) 8.18 (d,  $J=8.59$  Hz, 1 H) 10.08 (br. s., 1 H) 13.03 (s, 1 H).

4-67 N-(5-Bromo-thiazolo[5,4-b]pyridin-2-yl)-3-cyclopentyl-2-[4-(4-methyl-piperazine-1-sulfonyl)-3-trifluoromethyl-phenyl]-propionamide: MS  $M+1$  661,  $^1\text{H}$  NMR (400 MHz, DMSO- $D_6$ )  $\delta$  ppm 1.07 - 1.16 (m, 2 H) 1.39 - 1.49 (m, 2 H) 1.52 - 1.64 (m, 3 H) 1.65 - 1.75 (m, 2 H) 1.80 - 1.89 (m, 1 H) 2.16 (s, 3 H) 2.18 - 2.25 (m, 1 H) 2.31 - 2.37 (m, 4 H) 3.14 - 3.20 (m, 4

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H) 4.20 (t,  $J=7.58$  Hz, 1 H) 7.68 (d,  $J=8.34$  Hz, 1 H) 7.92 (dd,  $J=8.34$ , 1.52 Hz, 1 H) 8.01 - 8.04 (m, 1 H) 8.04 - 8.08 (m, 2 H).

4-68 3-Cyclopentyl-2-[4-(4-methyl-piperazine-1-sulfonyl)-3-trifluoromethyl-phenyl]-N-[5-(4-methyl-piperazin-1-yl)-thiazolo[5,4-b]pyridin-2-yl]-propionamide: MS  $M+1$  680,  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  ppm 1.09 - 1.21 (m, 2 H) 1.45 (dd,  $J=7.33$ , 4.55 Hz, 2 H) 1.52 - 1.64 (m, 3 H) 1.70 (d,  $J=16.93$  Hz, 2 H) 1.82 (dt,  $J=13.45$ , 6.79 Hz, 1 H) 2.20 (t,  $J=14.40$  Hz, 1 H) 2.20 (d,  $J=13.64$  Hz, 1 H) 2.77 (br. s., 3 H) 2.81 (d,  $J=4.80$  Hz, 3 H) 3.09 (br. s., 4 H) 3.15 (br. s., 3 H) 3.26 (br. s., 3 H) 3.39 (br. s., 4 H) 3.83 (br. s., 2 H) 4.24 (t,  $J=7.58$  Hz, 1 H) 4.40 (d,  $J=14.40$  Hz, 2 H) 7.09 (d,  $J=9.35$  Hz, 1 H) 7.96 (d,  $J=8.84$  Hz, 2 H) 8.06 (d,  $J=1.52$  Hz, 1 H) 8.12 (d,  $J=8.34$  Hz, 1 H).

4-69 2-[3-Chloro-4-(4-methyl-piperazine-1-sulfonyl)-phenyl]-3-cyclopentyl-N-(5-pyridin-4-yl-thiazolo[5,4-b]pyridin-2-yl)-propionamide: MS  $M+1$  625,  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  ppm 1.15 (d,  $J=11.62$  Hz, 2 H) 1.23 (s, 1 H) 1.40 - 1.50 (m, 2 H) 1.53 - 1.65 (m, 3 H) 1.75 (d,  $J=10.61$  Hz, 2 H) 1.81 - 1.90 (m, 1 H) 2.13 - 2.24 (m, 1 H) 2.78 (s, 3 H) 3.12 (d,  $J=6.32$  Hz, 3 H) 3.43 (br. s., 3 H) 3.85 (br. s., 2 H) 4.20 (t,  $J=7.58$  Hz, 1 H) 7.64 (dd,  $J=8.34$ , 1.77 Hz, 1 H) 7.78 (d,  $J=1.52$  Hz, 1 H) 8.01 (d,  $J=8.08$  Hz, 1 H) 8.27 - 8.35 (m, 1 H) 8.37 - 8.47 (m, 3 H) 8.86 (d,  $J=6.57$  Hz, 2 H) 10.52 (br. s., 1 H) 13.13 (s, 1 H).

4-70 3-Cyclopentyl-N-[5-(2-cyclopropyl-pyridin-4-yl)-thiazolo[5,4-b]pyridin-2-yl]-2-[4-(4-methyl-piperazine-1-sulfonyl)-phenyl]-propionamide: MS  $M+1$  631,  $^1\text{H}$  NMR (400 MHz, DMSO- $D_6$ )  $\delta$  ppm 0.94 - 1.00 (m, 4 H) 1.09 - 1.19 (m, 2 H) 1.39 - 1.50 (m, 2 H) 1.53 - 1.64 (m, 3 H) 1.72 (d,  $J=11.62$  Hz, 2 H) 1.84 (ddd,  $J=13.64$ , 7.20, 6.95 Hz, 1 H) 2.10 (s, 3 H) 2.17 - 2.28 (m, 2 H) 2.33 (s, 4 H) 2.88 (s, 4 H) 4.15 (t,  $J=7.58$  Hz, 1 H) 7.67 - 7.72 (m, 2 H) 7.72 - 7.76 (m, 2 H) 7.81 (dd,  $J=5.31$ , 1.77 Hz, 1 H) 8.01 (s, 1 H) 8.19 - 8.24 (m, 2 H) 8.50 (d,  $J=5.30$  Hz, 1 H).

4-71 N-(5-Chloro-thiazolo[5,4-b]pyridin-2-yl)-3-cyclohexyl-2-[4-(4-methyl-piperazine-1-sulfonyl)-phenyl]-propionamide: MS  $M+1$  563,  $^1\text{H}$  NMR (400 MHz, DMSO- $D_6$ )  $\delta$  ppm 0.88 - 1.00 (m, 2 H) 1.06 - 1.17 (m, 6 H) 1.55 - 1.81 (m, 5 H) 2.05 - 2.12 (m, 1 H) 2.72 (s, 4 H) 3.13 (m, 1 H) 3.38 (m, 4 H) 3.74 (m, 1 H) 4.28 (t,  $J=7.0$  Hz, 1 H) 7.57 (d,  $J=8.6$  Hz, 1 H) 7.71 (d,  $J=8.5$  Hz, 2 H) 7.79 (d,  $J=8.5$  Hz, 2 H) 8.17 (d,  $J=8.6$  Hz, 1 H).

4-72 2-[3-Chloro-4-(4-methyl-piperazine-1-sulfonyl)-phenyl]-3-cyclopentyl-N-[5-(4-methyl-piperazin-1-yl)-thiazolo[5,4-b]pyridin-2-yl]-propionamide: MS M+1 646, <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ ppm 1.08-1.19 (m, 2H) 1.39-1.49 (m, 2H) 1.53-1.62 (m, 3H) 1.65-1.75 (m, 2H) 1.76-1.84 (m, 1H) 2.09-2.20 (m, 1H) 2.81 (s, 3H) 2.86 (s, 3H) 2.9-3.2 (m, 8H) 3.42-3.9 (m, 6H) 4.05-4.13 (m, 1H) 4.36-4.47 (m, 2H) 7.09 (d, *J*=8.43 Hz, 1H) 7.61 (dd, *J*=8.43 Hz, 1.77 Hz, 1H) 7.74 (s, 1H) 7.94-8.01 (m, 2H).

4-73 (S)-4-{4-[2-Cyclopentyl-1-(5-pyridin-4-yl-thiazolo[5,4-b]pyridin-2-ylcarbamoyl)-ethyl]-benzenesulfonyl}-1-methyl-piperazine-2-carboxylic acid: MS M+1 635, <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ ppm 1.17 (d, *J*=8.34 Hz, 2 H) 1.45 (dd, *J*=7.33, 4.80 Hz, 2 H) 1.58 (d, *J*=5.05 Hz, 2 H) 1.62 (d, *J*=7.33 Hz, 1 H) 1.73 (br. s., 2 H) 1.80 - 1.88 (m, 1 H) 2.18 (s, 1 H) 2.69 (s, 3 H) 2.99 (br. s., 1 H) 3.36 (br. s., 2 H) 3.54 (br. s., 1 H) 3.97 (br. s., 1 H) 4.12 - 4.22 (m, 1 H) 7.72 (d, *J*=8.34 Hz, 2 H) 7.79 - 7.84 (m, 2 H) 8.25 - 8.33 (m, 4 H) 8.79 (d, *J*=6.32 Hz, 1 H) 13.04 (s, 1 H).

4-74 3-Cyclopentyl-2-[4-((S)-3,4-dimethyl-piperazine-1-sulfonyl)-phenyl]-N-(5-pyridin-4-yl-thiazolo[5,4-b]pyridin-2-yl)-propionamide: MS M+1 605, <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) □ ppm 0.92 (d, *J*=6.06 Hz, 3 H) 1.10 - 1.20 (m, 3 H) 1.39 - 1.48 (m, 2 H) 1.53 - 1.65 (m, 1 H) 1.66 - 1.75 (m, 2 H) 1.79 - 1.88 (m, 1 H) 1.99 (s, 2 H) 2.00 - 2.07 (m, 1 H) 2.11 - 2.23 (m, 2 H) 2.30 - 2.40 (m, 1 H) 2.66 - 2.74 (m, 1 H) 3.28 - 3.32 (m, 3 H) 3.34 - 3.42 (m, 2 H) 4.15 (t, *J*=7.58 Hz, 1 H) 7.67 - 7.76 (m, 4 H) 8.05 - 8.12 (m, 2 H) 8.23 (s, 2 H) 8.66 - 8.72 (m, 2 H) 12.98 (br. s., 1 H).

4-75 3-Cyclopentyl-2-[4-((S)-3,4-dimethyl-piperazine-1-sulfonyl)-phenyl]-N-(5-morpholin-4-yl-thiazolo[5,4-b]pyridin-2-yl)-propionamide: MS M+1 613, <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ ppm 1.13 (br. s., 2 H) 1.25 (d, *J*=6.32 Hz, 3 H) 1.44 (d, *J*=4.55 Hz, 2 H) 1.52 - 1.63 (m, 3 H) 1.74 (d, *J*=11.37 Hz, 2 H) 1.79 (d, *J*=5.31 Hz, 1 H) 2.09 - 2.18 (m, 1 H) 2.20 (br. s., 1 H) 2.40 (br. s., 1 H) 2.59 - 2.68 (m, 2 H) 2.74 (d, *J*=4.55 Hz, 6 H) 3.21 (d, *J*=3.79 Hz, 1 H) 3.39 (br. s., 1 H) 3.40 - 3.51 (m, 5 H) 3.66 - 3.74 (m, 4 H) 4.09 - 4.16 (m, 1 H) 6.98 (d, *J*=9.09 Hz, 1 H) 7.71 (d, *J*=8.59 Hz, 2 H) 7.75 - 7.81 (m, 2H) 7.88 (d, *J*=9.09 Hz, 1 H) 12.57 (s, 1 H).

4-76 (S)-4-{4-[2-Cyclopentyl-1-(5-pyridin-4-yl-thiazolo[5,4-b]pyridin-2-ylcarbamoyl)-ethyl]-benzenesulfonyl}-1-methyl-piperazine-2-carboxylic acid methyl ester: MS M+1 649, <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ ppm 1.13 (br. s., 2 H) 1.18 (t, *J*=7.07 Hz, 1 H) 1.42 (br. s., 1 H) 1.45

(dd,  $J=7.20, 4.67$  Hz, 1 H) 1.52 - 1.62 (m, 1 H) 1.63 (s, 1 H) 1.70 (br. s., 1 H) 1.72 (d,  $J=5.31$  Hz, 1 H) 1.79 - 1.89 (m, 1 H) 2.15 - 2.24 (m, 3 H) 2.34 (d,  $J=7.33$  Hz, 1 H) 2.87 (br. s., 1 H) 2.92 - 3.00 (m, 2 H) 3.08 (d,  $J=3.28$  Hz, 1 H) 3.18 (dd,  $J=6.69, 3.41$  Hz, 1 H) 3.27 - 3.33 (m, 2 H) 3.62 (s, 3 H) 4.15 (s, 1 H) 7.69 (s, 1 H) 7.71 (d,  $J=1.26$  Hz, 1 H) 7.72 - 7.78 (m, 2 H) 8.06 - 8.12 (m, 2 H) 8.24 (s, 2 H) 8.66 - 8.72 (m, 2 H) 12.97 (s, 1 H).

4-77 (R)-4-{4-[2-Cyclopentyl-1-(5-pyridin-4-yl-thiazolo[5,4-b]pyridin-2-ylcarbamoyl)-ethyl]-benzenesulfonyl}-1-methyl-piperazine-2-carboxylic acid methyl ester: MS  $M+1$  649,  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ )  $\delta$  ppm 1.17 (t,  $J=7.20$  Hz, 3 H) 1.43 (br. s., 1 H) 1.45 (d,  $J=2.53$  Hz, 1 H) 1.57 (br. s., 2 H) 1.63 (s, 1 H) 1.72 (br. s., 2 H) 1.80 - 1.89 (m, 1 H) 2.15 - 2.24 (m, 4 H) 2.29 - 2.36 (m, 1 H) 2.94 (d,  $J=7.58$  Hz, 3 H) 3.08 (br. s., 1 H) 3.18 (dd,  $J=6.69, 3.41$  Hz, 1 H) 3.29 (s, 4 H) 3.62 (s, 3 H) 4.12 - 4.18 (m, 1 H) 7.66 - 7.72 (m, 2 H) 7.73 - 7.77 (m, 2 H) 8.08 - 8.12 (m, 2 H) 8.23 (s, 2 H) 8.66 - 8.72 (m, 2 H) 12.97 (s, 1 H).

4-78 (R)-4-{4-[2-Cyclopentyl-1-(5-pyridin-4-yl-thiazolo[5,4-b]pyridin-2-ylcarbamoyl)-ethyl]-benzenesulfonyl}-1-methyl-piperazine-2-carboxylic acid: MS  $M+1$  635,  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ )  $\delta$  ppm 1.11 - 1.22 (m, 2 H) 1.45 (dd,  $J=7.33, 4.80$  Hz, 2 H) 1.56 (br. s., 1 H) 1.57 - 1.60 (m, 1 H) 1.60 - 1.65 (m, 1 H) 1.68 - 1.78 (m, 2 H) 1.84 (ddd,  $J=13.58, 7.07, 6.88$  Hz, 1 H) 2.20 (ddd,  $J=13.52, 7.83, 7.45$  Hz, 1 H) 2.75 (s, 3 H) 2.88 (br. s., 1 H) 3.10 (br. s., 1 H) 3.43 (br. s., 2 H) 3.58 (br. s., 1 H) 4.18 (t,  $J=7.45$  Hz, 2 H) 7.73 (d,  $J=8.34$  Hz, 2 H) 7.79 - 7.86 (m, 2 H) 8.28 - 8.32 (m, 1 H) 8.33 - 8.40 (m, 3 H) 8.83 (d,  $J=6.32$  Hz, 2 H) 13.08 (s, 1 H).

4-79 2-((R)-3-Cyclopentyl-2-[4-(2-methoxy-ethylsulfamoyl)-phenyl]-propionylamino)-benzothiazole-6-carboxylic acid: MS  $M+1$  533,  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ )  $\delta$  ppm 1.04 - 1.16 (m, 2 H) 1.41 (dd,  $J=7.07, 4.80$  Hz, 1 H) 1.38 (br. s., 1 H) 1.57 (br. s., 1 H) 1.54 (dd,  $J=6.19, 2.65$  Hz, 1 H) 1.63 (br. s., 1 H) 1.60 (d,  $J=7.33$  Hz, 2 H) 1.72 (br. s., 1 H) 1.68 (dd,  $J=13.14, 6.32$  Hz, 8 H) 2.04 - 2.12 (m, 1 H) 2.07 (s, 3 H) 2.85 (t,  $J=5.94$  Hz, 2 H) 3.13 (s, 3 H) 3.26 (t,  $J=5.94$  Hz, 2 H) 3.60 (t,  $J=7.58$  Hz, 1 H) 7.13 (d,  $J=8.34$  Hz, 1 H) 7.54 (d,  $J=8.34$  Hz, 3 H) 7.60 - 7.67 (m, 3 H) 7.99 (d,  $J=1.52$  Hz, 1 H).

4-80 2-((R)-3-Cyclopentyl-2-[4-[(2-methoxy-ethyl)-methyl-sulfamoyl]-phenyl]-propionylamino)-benzothiazole-6-carboxylic acid: MS  $M+1$  547,  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-D_6$ )  $\delta$  ppm 1.04 - 1.16 (m, 2 H) 1.35 - 1.47 (m, 2 H) 1.52 - 1.59 (m, 2 H) 1.62 - 1.72 (m, 3 H)

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2.05 - 2.15 (m, 1 H) 2.07 (s, 3H) 2.86 (s, 3 H) 3.10 (t, J=5.68 Hz, 2 H) 3.19 (s, 3 H) 3.41 (t, J=5.56 Hz, 2 H) 3.62 (t, J=7.45 Hz, 1 H) 7.13 (d, J=8.59 Hz, 1 H) 7.59 - 7.66 (m, 4 H) 7.99 (m, 1H).

4-81 (R)-N-(5-Chloro-thiazolo[5,4-b]pyridin-2-yl)-3-cyclopentyl-2-[4-(2-methoxy-ethylsulfamoyl)-phenyl]-propionamide: MS M+1 523, <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ ppm 1.08 - 1.20 (m, 2 H) 1.38 - 1.48 (m, 2 H) 1.51 - 1.62 (m, 3 H) 1.70 (br. s., 2 H) 1.75 - 1.86 (m, 1 H) 2.10 - 2.20 (m, 1 H) 2.89 (q, J=5.73 Hz, 2 H) 3.09 (s, 3 H) 3.25 (t, J=5.81 Hz, 2 H) 4.09 (t, J=7.58 Hz, 1 H) 7.58 (dd, J=17.18, 8.34 Hz, 3 H) 7.69 (t, J=5.81 Hz, 1 H) 7.78 (d, J=8.59 Hz, 2 H) 8.15 (d, J=8.34 Hz, 1 H) 12.95 (s, 1 H).

4-82 N-(5-Bromo-thiazolo[5,4-b]pyridin-2-yl)-3-cyclopentyl-2-[4-(4-methyl-4,7-diaza-spiro[2.5]octane-7-sulfonyl)-phenyl]-propionamide: MS M+1 619, <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ ppm 0.44 (d, J=10.86 Hz, 1 H) 0.44 (d, J=1.77 Hz, 1 H) 0.58 (d, J=10.86 Hz, 1 H) 0.58 (d, J=1.52 Hz, 1 H) 1.12 (td, J=8.21, 4.80 Hz, 2 H) 1.05 - 1.15 (m, 1 H) 1.43 (dd, J=7.33, 4.80 Hz, 2 H) 1.51 - 1.62 (m, 3 H) 1.69 (dd, J=11.49, 4.93 Hz, 2 H) 1.82 (t, J=13.89 Hz, 1 H) 1.82 (d, J=13.39 Hz, 1 H) 2.03 (s, 3 H) 2.17 (ddd, J=13.33, 7.58, 7.39 Hz, 1 H) 2.73 (s, 2 H) 2.79 (d, J=5.56 Hz, 2 H) 2.77 (br. s., 1 H) 2.90 (d, J=5.81 Hz, 2 H) 4.11 (t, J=7.58 Hz, 1 H) 7.68 (d, J=2.78 Hz, 2 H) 7.66 (d, J=2.78 Hz, 1 H) 7.71 - 7.75 (m, 2 H) 8.04 (d, J=8.59 Hz, 1 H).

4-83 3-Cyclopentyl-2-[4-(4-methyl-4,7-diaza-spiro[2.5]octane-7-sulfonyl)-phenyl]-N-(5-pyridin-4-yl-thiazolo[5,4-b]pyridin-2-yl)-propionamide: MS M+1 617, <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ ppm 0.44 (d, J=10.86 Hz, 1 H) 0.44 (d, J=1.77 Hz, 1 H) 0.58 (d, J=10.86 Hz, 1 H) 0.58 (d, J=1.52 Hz, 1 H) 1.12 (td, J=8.21, 4.80 Hz, 2 H) 1.05 - 1.15 (m, 1 H) 1.43 (dd, J=7.33, 4.80 Hz, 2 H) 1.51 - 1.62 (m, 3 H) 1.69 (dd, J=11.49, 4.93 Hz, 2 H) 1.82 (t, J=13.89 Hz, 1 H) 1.82 (d, J=13.39 Hz, 1 H) 1.99 (s, 1 H) 2.17 (ddd, J=13.33, 7.58, 7.39 Hz, 1 H) 2.73 (s, 2 H) 2.79 (d, J=5.56 Hz, 2 H) 2.77 (br. s., 1 H) 2.90 (d, J=5.81 Hz, 2 H) 4.11 (t, J=7.58 Hz, 1 H) 7.68 (d, J=2.78 Hz, 2 H) 7.66 (d, J=2.78 Hz, 1 H) 7.71 - 7.75 (m, 2 H) 8.04 (d, J=8.59 Hz, 1 H).

4-84 3-Cyclopentyl-2-[4-(4-methyl-4,7-diaza-spiro[2.5]octane-7-sulfonyl)-phenyl]-N-[5-(4-methyl-piperazin-1-yl)-thiazolo[5,4-b]pyridin-2-yl]-propionamide: MS M+1 638, <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ ppm 0.70-1.2 (m, 6H) 1.38-1.49 (m, 2H) 1.52-1.63 (m, 3H) 1.67-1.83 (m,

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3H) 2.11-2.21 (m, 1H) 2.85 (s, 3H) 3.12-3.64 (m, 4H) 4.05-4.15 (m, 1H) 4.36-4.46 (m, 2H) 7.09 (d,  $J=9.09$  Hz, 1H) 7.66-7.72 (m, 2H) 7.96 (d,  $J=9.09$  Hz, 1H).

4-85 (R)-3-Cyclopentyl-2-[4-(4-methyl-4,7-diaza-spiro[2.5]octane-7-sulfonyl)-phenyl]-N-(5-pyridin-4-yl-thiazolo[5,4-b]pyridin-2-yl)-propionamide: MS  $M+1$  617,  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  ppm 0.41-0.46 (m, 2H) 0.55-0.60 (m, 2H) 1.38-1.48 (m, 3H) 1.54-1.63 (m, 3H) 1.67-1.75 (m, 3H) 1.80-1.88 (m, 1H) 2.12 (s, 3H) 2.14-2.24 (m, 1H) 2.73 (s, 2H) 2.77-2.80 (m, 2H) 2.88-2.94 (m, 2H) 4.12-4.18 (m, 1H) 7.67-7.72 (m, 2H) 7.74-7.78 (m, 2H) 8.08-8.12 (m, 2H) 8.23 (s, 2H) 8.68-8.72 (m, 2H).

4-86 3-Cyclopentyl-N-(5-pyridin-4-yl-thiazolo[5,4-b]pyridin-2-yl)-2-[4-(3,3,4-trimethyl-piperazine-1-sulfonyl)-phenyl]-propionamide: MS  $M+1$  619,  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  ppm 1.17 (br. s., 2 H) 1.30 (d,  $J=7.58$  Hz, 6 H) 1.45 (d,  $J=2.53$  Hz, 2 H) 1.59 (br. s., 3 H) 1.74 (br. s., 2 H) 1.83 (br. s., 1 H) 2.19 (br. s., 1 H) 2.41 (br. s., 2 H) 2.67 (br. s., 3 H) 3.33 - 3.44 (m, 2 H) 3.63 (br. s., 4 H) 4.18 (br. s., 1 H) 7.72 - 7.83 (m, 4 H) 8.22 - 8.33 (m, 4 H) 8.77 (d,  $J=5.05$  Hz, 2 H) 9.47 (br. s., 1 H) 13.04 (s, 1H).

4-87 2-(4-Butyrylsulfamoyl-phenyl)-3-cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide: MS  $M+1$  531,  $^1\text{H}$  NMR (400 MHz, DMSO- $D_6$ )  $\delta$  ppm 0.75 (t,  $J=7.45$  Hz, 4 H) 1.13 (s, 3 H) 1.36 - 1.47 (m, 5 H) 1.52 - 1.63 (m, 5 H) 1.76 (ddd,  $J=13.52, 6.95, 6.82$  Hz, 5 H) 1.82 (s, 1 H) 1.85 (t,  $J=7.33$  Hz, 4 H) 2.09 (ddd,  $J=13.26, 7.71, 7.58$  Hz, 2 H) 3.87 - 3.93 (m, 6 H) 6.84 (d,  $J=8.84$  Hz, 2 H) 7.33 - 7.36 (m, 3 H) 7.63 - 7.67 (m, 3 H).

4-88 3-Cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-2-{4-[4-(2-oxo-2-piperidin-1-yl-ethyl)-piperazine-1-sulfonyl]-phenyl}-propionamide: MS  $M+1$  655,  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  ppm 1.23 (br. s., 5 H) 1.41 (br. s., 4 H) 1.55 (br. s., 3 H) 1.70 (br. s., 2 H) 2.44 (br. s., 6 H) 2.84 (br. s., 4 H) 3.07 (s, 2 H) 3.24 (br. s., 4 H) 3.90 (s, 3 H) 4.05 (s, 2 H) 6.91 (s, 1 H) 7.70 (d,  $J=14.15$  Hz, 4 H) 8.02 (s, 1 H) 12.63 (s, 1 H).

4-89 3-Cyclopentyl-2-{4-[4-(isopropylcarbamoyl-methyl)-piperazine-1-sulfonyl]-phenyl}-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide: MS  $M+1$  629,  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  ppm 0.95 (d,  $J=6.57$  Hz, 6 H) 1.11 (d,  $J=3.54$  Hz, 1 H) 1.44 (dd,  $J=7.20, 4.67$  Hz, 2 H) 1.51 - 1.63 (m, 4 H) 1.68 - 1.76 (m, 2 H) 2.13 - 2.20 (m, 1 H) 2.45 (br. s., 2 H) 2.46 (d,  $J=4.55$  Hz, 3 H) 2.83 (s, 2 H) 2.93 (br. s., 4 H) 3.80 (dd,  $J=14.65, 6.82$  Hz, 1 H) 3.90 (s, 3 H)



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4.09 (d,  $J=14.91$  Hz, 1 H) 6.90 (d,  $J=8.84$  Hz, 1 H) 7.37 (d,  $J=8.08$  Hz, 1 H) 7.65 - 7.69 (m, 2 H) 7.72 - 7.76 (m, 2 H) 8.02 (d,  $J=8.84$  Hz, 1 H) 12.66 (br. s., 1 H).

1-{4-[2-Cyclopentyl-1-(5-methoxy-thiazolo[5,4-b]pyridin-2-ylcarbamoyl)-ethyl]-benzenesulfonyl}-piperidine-4-carboxylic acid: MS  $M+1$  573,  $^1\text{H}$  NMR (400 MHz, DMSO- $D_6$ )  $\delta$  ppm 1.05 - 1.16 (m, 2 H) 1.36 - 1.47 (m, 2 H) 1.49 - 1.61 (m, 5 H) 1.66 - 1.72 (m, 3 H) 1.75 (s, 1 H) 1.78 - 1.80 (m, 1 H) 1.92 - 2.02 (m, 1 H) 2.08 - 2.18 (m, 1 H) 2.40 (t,  $J=9.85$  Hz, 2 H) 3.35 (d,  $J=11.37$  Hz, 2 H) 3.82 - 3.92 (m, 4 H) 6.74 (d,  $J=8.59$  Hz, 1 H) 7.59 - 7.67 (m, 4 H) 7.79 (d,  $J=8.84$  Hz, 1 H).

4-90 1-{4-[2-Cyclopentyl-1-(5-methoxy-thiazolo[5,4-b]pyridin-2-ylcarbamoyl)-ethyl]-benzenesulfonyl}-piperidine-3-carboxylic acid: MS  $M+1$  573,  $^1\text{H}$  NMR (400 MHz, CHLOROFORM- $d$ )  $\delta$  ppm 1.08 (br. s., 2 H) 1.18 (t,  $J=7.20$  Hz, 1 H) 1.42 (br. s., 3 H) 1.54 (br. s., 2 H) 1.66 (d,  $J=14.15$  Hz, 2 H) 1.61 (d,  $J=7.83$  Hz, 2 H) 1.78 (br. s., 1 H) 1.83 (dd,  $J=13.26, 6.69$  Hz, 1 H) 1.89 - 2.00 (m, 1 H) 2.23 (d,  $J=6.32$  Hz, 1 H) 2.65 (br. s., 2 H) 2.77 (br. s., 1 H) 3.41 (s, 1 H) 3.78 (d,  $J=6.06$  Hz, 2 H) 3.91 (s, 4 H) 6.71 (dd,  $J=8.72, 3.41$  Hz, 1 H) 7.55 (t,  $J=7.45$  Hz, 2 H) 7.65 (dd,  $J=8.21, 4.93$  Hz, 1 H) 7.71 (br. s., 2 H).

4-91 ((S)-1-{4-[2-Cyclopentyl-1-(5-methoxy-thiazolo[5,4-b]pyridin-2-ylcarbamoyl)-ethyl]-benzenesulfonyl}-pyrrolidin-2-yl)-acetic acid: MS  $M+1$  573,  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  ppm 1.09 (br. s., 2 H) 1.39 (br. s., 4 H) 1.54 (br. s., 4 H) 1.70 (br. s., 4 H) 2.11 (br. s., 2 H) 3.05 (br. s., 1 H) 3.26 (br. s., 3 H) 3.85 (s, 5 H) 6.71 (s, 1 H) 7.63 (s, 2 H) 7.70 (s, 2 H) 7.75 (s, 1 H).

4-92 4-{4-[2-Cyclopentyl-1-(5-methoxy-thiazolo[5,4-b]pyridin-2-ylcarbamoyl)-ethyl]-benzenesulfonyl}-piperazine-2-carboxylic acid: MS  $M+1$  574,  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  ppm 1.05 - 1.17 (m, 1 H) 1.11 (d,  $J=4.29$  Hz, 1 H) 1.42 (dd,  $J=7.07, 4.80$  Hz, 2 H) 1.51 - 1.63 (m, 3 H) 1.70 (dd,  $J=12.88, 6.57$  Hz, 3 H) 1.88 (t,  $J=10.74$  Hz, 1 H) 2.02 - 2.14 (m, 2 H) 2.58 (t,  $J=11.75$  Hz, 1 H) 2.76 (d,  $J=9.60$  Hz, 1 H) 2.89 (d,  $J=11.87$  Hz, 1 H) 3.63 (d,  $J=10.11$  Hz, 1 H) 3.81 (d,  $J=7.58$  Hz, 1 H) 3.85 (s, 3 H) 6.68 (d,  $J=8.59$  Hz, 1 H) 7.57 - 7.66 (m, 4 H) 7.71 (d,  $J=8.08$  Hz, 1 H).

4-93 1-{4-[2-Cyclopentyl-1-(5-methoxy-thiazolo[5,4-b]pyridin-2-ylcarbamoyl)-ethyl]-benzenesulfonyl}-4-methyl-piperazine-2-carboxylic acid: MS  $M+1$  588,  $^1\text{H}$  NMR (400 MHz,

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DMSO-d<sub>6</sub>)  $\delta$  ppm 1.14 (br. s., 2 H) 1.43 (d, J=4.80 Hz, 2 H) 1.60 1.57 (t, J=7.58 Hz, 3 H) 1.78 (dd, J=13.77, 6.95 Hz, 3 H) 2.15 (d, J=13.64 Hz, 2 H) 3.91 (s, 5H) 4.08 - 4.19 (m, 2 H) 4.45 (br. s., 2 H) 6.91 (d, J=8.84 Hz, 1 H) 7.62 (d, J=8.08 Hz, 2 H) 7.81 (d, J=8.34 Hz, 2 H) 8.03 (d, J=8.59 Hz, 1 H) 12.72 (s, 1 H).

4-94 1-{4-[2-Cyclopentyl-1-(5-methoxy-thiazolo[5,4-b]pyridin-2-ylcarbamoyl)-ethyl]-benzenesulfonyl}-piperazine-2-carboxylic acid: MS M+1 574, <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>)  $\delta$  ppm 1.08 - 1.19 (m, 2 H) 1.13 (dd, J=11.24, 5.43 Hz, 2 H) 1.44 (dd, J=7.20, 4.67 Hz, 2 H) 1.51 - 1.63 (m, 3 H) 1.73 (td, J=14.21, 6.95 Hz, 3 H) 2.15 (d, J=12.88 Hz, 1 H) 2.42 (td, J=11.94, 3.41 Hz, 1 H) 2.68 (dd, J=12.13, 4.29 Hz, 1 H) 2.83 (d, J=11.12 Hz, 1 H) 3.38 (br. s., 2 H) 3.52 (s, 1 H) 3.91 (s, 3 H) 4.07 (t, J=7.58 Hz, 1 H) 4.30 (d, J=3.28 Hz, 1 H) 6.91 (d, J=8.84 Hz, 1 H) 7.57 (d, J=7.83 Hz, 2 H) 7.79 (d, J=8.34 Hz, 2 H) 8.02 (d, J=8.59 Hz, 1 H). EC<sub>50</sub> in primary enzyme assay 9.3 $\mu$ M

4-95 1-{4-[2-Cyclopentyl-1-(5-methoxy-thiazolo[5,4-b]pyridin-2-ylcarbamoyl)-ethyl]-benzenesulfonyl}-pyrrolidine-3-carboxylic acid: MS M+1 559, <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>)  $\delta$  ppm 1.10 (br. s., 3 H) 1.43 (br. s., 3 H) 1.54 (br. s., 3 H) 1.73 (s, 5 H) 2.13 (br. s., 1 H) 3.07 (s, 2 H) 3.21 (s, 2 H) 3.87 (s, 4 H) 3.96 (br. s., 1 H) 6.79 (s, 1 H) 7.61 (s, 2 H) 7.71 (s, 2 H) 7.85 (s, 1 H).

4-96 4-{4-[2-Cyclopentyl-1-(5-methoxy-thiazolo[5,4-b]pyridin-2-ylcarbamoyl)-ethyl]-benzenesulfonyl}-1-methyl-piperazine-2-carboxylic acid: MS M+1 588, <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>)  $\delta$  ppm 1.07 - 1.19 (m, 2 H) 1.44 (dd, J=7.33, 4.80 Hz, 2 H) 1.58 (dq, J=15.22, 7.64 Hz, 2 H) 1.56 (br. s., 2 H) 1.70 (dd, J=6.82, 4.55 Hz, 2 H) 1.81 (ddd, J=13.58, 7.07, 6.88 Hz, 1 H) 2.16 (ddd, J=13.26, 7.71, 7.58 Hz, 1 H) 2.31 (s, 3 H) 2.42 (t, J=8.21 Hz, 1 H) 2.75 (t, J=8.08 Hz, 1 H) 2.83 (dd, J=10.86, 7.83 Hz, 1 H) 2.98 - 3.10 (m, 3 H) 3.19 (d, J=11.12 Hz, 1 H) 3.91 (s, 3 H) 4.10 (t, J=7.58 Hz, 1 H) 6.91 (d, J=8.59 Hz, 1 H) 7.66 - 7.71 (m, 2 H) 7.73 - 7.78 (m, 2 H) 8.03 (d, J=8.84 Hz, 1 H) 12.68 (s, 1 H).

4-97 {2-[3-Cyclopentyl-2-(4-diethylsulfamoyl-phenyl)-propionylamino]-thiazolo[5,4-b]pyridin-5-yloxy}-acetic acid: MS M+1 561, <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>)  $\delta$  ppm 1.03 (t, J=7.07 Hz, 6 H) 1.07 - 1.18 (m, 2 H) 1.43 (dd, J=7.20, 4.67 Hz, 2 H) 1.56 (t, J=7.33 Hz, 3 H) 1.69 (d, J=6.32 Hz, 2 H) 1.79 (ddd, J=13.58, 7.07, 6.88 Hz, 1 H) 2.15 (dd, J=7.20, 5.43 Hz, 1 H) 3.14

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(q, J=7.07 Hz, 4 H) 4.07 (t, J=7.58 Hz, 1 H) 4.88 (s, 2 H) 6.99 (d, J=8.84 Hz, 1 H) 7.61 (d, J=8.34 Hz, 2 H) 7.78 (d, J=8.59 Hz, 2 H) 8.06 (d, J=8.84 Hz, 1 H) 12.68 (br. s., 1 H).

4-98 N-(5-Carbamoylmethoxy-thiazolo[5,4-b]pyridin-2-yl)-3-cyclopentyl-2-(4-diethylsulfamoyl-phenyl)-propionamide: MS M+1 560, <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm 1.03 (t, J=7.20 Hz, 6 H) 1.12 (d, J=11.62 Hz, 2 H) 1.43 (dd, J=7.07, 4.80 Hz, 2 H) 1.59 (br. s., 1 H) 1.57 (d, J=7.33 Hz, 2 H) 1.70 (br. s., 2 H) 1.79 (ddd, J=13.58, 7.07, 6.88 Hz, 1 H) 2.13 (t, J=7.58 Hz, 1 H) 3.14 (q, J=7.07 Hz, 4 H) 4.07 (t, J=7.58 Hz, 1 H) 4.71 (s, 2 H) 6.99 (d, J=8.84 Hz, 1 H) 7.18 - 7.27 (m, 1 H) 7.50 (br. s., 1 H) 7.61 (d, J=8.34 Hz, 2 H) 7.78 (d, J=8.34 Hz, 2 H) 8.06 (d, J=8.84 Hz, 1 H) 12.68 (s, 1 H).

4-99 3-(4-{4-[2-Cyclopentyl-1-(5-methoxy-thiazolo[5,4-b]pyridin-2-ylcarbamoyl)-ethyl]-benzenesulfonylamino}-piperidin-1-yl)-propionic acid: MS M+1 617

4-100 (R)-1-{4-[2-Cyclopentyl-1-(5-methoxy-thiazolo[5,4-b]pyridin-2-ylcarbamoyl)-ethyl]-benzenesulfonyl}-piperidine-2-carboxylic acid: MS M+1 573, <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm 1.06 (br. s., 4 H) 1.23 (br. s., 2 H) 1.38 (br. s., 5 H) 1.70 (br. s., 4 H) 2.06 (br. s., 3 H) 3.45 (br. s., 1 H) 3.87 (s, 5 H) 4.05 (br. s., 1 H) 6.77 (br. s., 1 H) 7.50 (s, 3 H) 7.82 (br. s., 3 H).

4-101 (S)-1-{4-[2-Cyclopentyl-1-(5-methoxy-thiazolo[5,4-b]pyridin-2-ylcarbamoyl)-ethyl]-benzenesulfonyl}-piperidine-2-carboxylic acid: MS M+1 573, <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm 1.08 (br. s., 3 H) 1.22 (br. s., 2 H) 1.35 (br. s., 5 H) 1.55 (br. s., 4 H) 1.69 (br. s., 4 H) 2.09 (br. s., 3 H) 3.87 (s, 4 H) 4.05 (br. s., 1 H) 6.78 (br. s., 1 H) 7.50 (s, 2 H) 7.81 (br. s., 3 H).

4-102 3-(4-{4-[2-Cyclopentyl-1-(5-methoxy-thiazolo[5,4-b]pyridin-2-ylcarbamoyl)-ethyl]-benzenesulfonyl}-piperazin-1-yl)-propionic acid: MS M+1 602, <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm 1.11 (br. s., 3 H) 1.55 (br. s., 4 H) 1.71 (br. s., 4 H) 2.09 - 2.20 (m, 4 H) 2.38 (br. s., 4 H) 2.84 (br. s., 4 H) 3.86 (s, 5 H) 6.76 (s, 1 H) 7.64 (s, 5 H) 7.79 (s, 1 H).

4-103 4-(4-{4-[2-Cyclopentyl-1-(5-methoxy-thiazolo[5,4-b]pyridin-2-ylcarbamoyl)-ethyl]-benzenesulfonyl}-piperazin-1-yl)-4-oxo-butyric acid: MS M+1 630, <sup>1</sup>H NMR (400 MHz, DMSO-D<sub>6</sub>) δ ppm 1.09 (td, J=8.46, 3.54 Hz, 2 H) 1.36 - 1.46 (m, 2 H) 1.50 - 1.61 (m, 3 H)

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1.63 - 1.72 (m, 3 H) 2.11 (t,  $J=7.20$  Hz, 3 H) 2.37 (t,  $J=7.07$  Hz, 2 H) 2.91 (s, 4 H) 3.49 (s, 6 H) 3.68 - 3.79 (m, 3 H) 3.84 (s, 4 H) 6.64 (d,  $J=8.59$  Hz, 1 H) 7.59 - 7.66 (m, 5 H)

4-104 3-Cyclopentyl-2-[4-((S)-3-methyl-piperazine-1-sulfonyl)-phenyl]-N-(5-morpholin-4-yl-thiazolo[5,4-b]pyridin-2-yl)-propionamide: MS  $M+1$  599,  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ )  $\delta$  ppm 1.10 - 1.20 (m, 5 H) 1.23 (br. s., 1 H) 1.40 - 1.50 (m, 2 H) 1.52 - 1.63 (m, 3 H) 1.76 (br. s., 3 H) 2.13 - 2.18 (m, 1 H) 2.20 (s, 1 H) 2.32 - 2.42 (m, 1 H) 3.10 (br. s., 1 H) 3.30 - 3.40 (m, 2 H) 3.44 - 3.51 (m, 4 H) 3.65 (br. s., 12 H) 3.70 (d,  $J=4.80$  Hz, 4 H) 3.72 (br. s., 1 H) 4.13 (t,  $J=7.45$  Hz, 1 H) 6.98 (d,  $J=9.09$  Hz, 1 H) 7.69 - 7.74 (m, 2 H) 7.76 - 7.81 (m, 2 H) 7.88 (d,  $J=9.09$  Hz, 1 H) 12.57 (s, 1 H).

4-105 3-Cyclopentyl-2-[4-((S)-3-methyl-piperazine-1-sulfonyl)-phenyl]-N-(5-pyridin-4-yl-thiazolo[5,4-b]pyridin-2-yl)-propionamide: MS  $M+1$  591,  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ )  $\delta$  ppm 1.14 (d,  $J=3.28$  Hz, 1 H) 1.15 - 1.24 (m, 4 H) 1.46 (dd,  $J=7.20, 4.67$  Hz, 2 H) 1.58 (t,  $J=7.33$  Hz, 2 H) 1.63 (d,  $J=7.07$  Hz, 1 H) 1.71 (br. s., 1 H) 1.74 (d,  $J=4.55$  Hz, 1 H) 1.83 (dd,  $J=13.52, 1.64$  Hz, 1 H) 2.15 - 2.25 (m, 1 H) 2.44 (br. s., 1 H) 3.09 (br. s., 1 H) 3.33 (br. s., 1 H) 3.39 (br. s., 1 H) 3.60 - 3.71 (m, 3 H) 4.25 (t,  $J=7.58$  Hz, 1 H) 7.71 - 7.77 (m, 2 H) 7.77 - 7.83 (m, 2 H) 8.33 (d,  $J=8.59$  Hz, 1 H) 8.39 - 8.45 (m, 1 H) 8.52 (d,  $J=5.81$  Hz, 2 H) 8.90 (d,  $J=6.57$  Hz, 2 H) 13.20 (s, 1 H).

4-106 3-Cyclopentyl-N-[5-(2-methoxy-ethylamino)-thiazolo[5,4-b]pyridin-2-yl]-2-[4-(piperazine-1-sulfonyl)-phenyl]-propionamide: MS  $M+1$  573,  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-D_6$ )  $\delta$  ppm 1.09 - 1.20 (m, 2 H) 1.39 - 1.49 (m, 2 H) 1.59 (qd,  $J=7.62, 7.45$  Hz, 3 H) 1.68 - 1.79 (m, 3 H) 2.11 - 2.21 (m, 1 H) 3.08 (d,  $J=4.80$  Hz, 4 H) 3.22 (s, 4 H) 3.27 (s, 3 H) 3.41 - 3.49 (m, 4 H) 4.09 (t,  $J=7.45$  Hz, 1 H) 6.63 (d,  $J=8.84$  Hz, 1 H) 7.67 - 7.74 (m, 3 H) 7.76 - 7.81 (m, 2 H) 8.52 (s, 2 H) 12.41 (s, 1 H).

4-107 3-Cyclopentyl-2-[4-(piperazine-1-sulfonyl)-phenyl]-N-(5-vinyl-thiazolo[5,4-b]pyridin-2-yl)-propionamide: MS  $M+1$  526,  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-D_6$ )  $\delta$  ppm 1.06 (s, 2 H) 1.35 (dd,  $J=7.07, 4.80$  Hz, 2 H) 1.43 - 1.54 (m, 3 H) 1.65 (d,  $J=8.34$  Hz, 2 H) 1.68 - 1.76 (m, 1 H) 2.07 (s, 1 H) 2.99 (d,  $J=4.80$  Hz, 4 H) 3.09 (s, 4 H) 4.06 (t,  $J=7.58$  Hz, 1 H) 5.40 (dd,  $J=10.99, 1.39$  Hz, 1 H) 6.14 (dd,  $J=17.43, 1.26$  Hz, 1 H) 6.80 (dd,  $J=17.43, 10.86$  Hz, 1 H) 7.54 (d,  $J=8.34$  Hz, 1 H) 7.61 - 7.67 (m, 2 H) 7.67 - 7.72 (m, 2 H) 7.97 (d,  $J=8.34$  Hz, 1 H) 8.42 (s, 2 H) 12.79 (s, 1 H).

4-108 3-Cyclopentyl-2-[4-(piperazine-1-sulfonyl)-phenyl]-N-(5-pyridin-4-yl-thiazolo[5,4-b]pyridin-2-yl)-propionamide: MS M+1 577, <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ ppm 1.17 (br. s., 2 H) 1.46 (br. s., 2 H) 1.58 (d, *J*=5.81 Hz, 3 H) 1.74 (br. s., 2 H) 1.84 (br. s., 1 H) 2.20 (br. s., 1 H) 3.13 (br. s., 7 H) 4.23 (br. s., 1 H) 7.73 - 7.84 (m, 4 H) 8.27 - 8.36 (m, 1 H) 8.41 (d, *J*=8.59 Hz, 1 H) 8.48 (br. s., 2 H) 8.88 (d, *J*=5.05 Hz, 4 H) 13.16 (br. s., 1 H).

4-109 3-Cyclopentyl-N-(5-morpholin-4-yl-thiazolo[5,4-b]pyridin-2-yl)-2-[4-(piperazine-1-sulfonyl)-phenyl]-propionamide: MS M+1 585, <sup>1</sup>H NMR (400 MHz, DMSO-*D*<sub>6</sub>) δ ppm 1.09 - 1.20 (m, 2 H) 1.45 (dd, *J*=7.07, 4.55 Hz, 2 H) 1.52 - 1.63 (m, 3 H) 1.77 (dd, *J*=13.52, 6.69 Hz, 3 H) 2.11 - 2.21 (m, 1 H) 3.12 (s, 4 H) 3.16 (s, 4 H) 3.42 - 3.50 (m, 4 H) 3.65 - 3.74 (m, 4 H) 4.14 (t, *J*=7.58 Hz, 1 H) 6.98 (d, *J*=9.09 Hz, 1 H) 7.69 - 7.75 (m, 2 H) 7.76 - 7.81 (m, 2 H) 7.89 (d, *J*=9.09 Hz, 1 H) 8.91 (s, 2 H) 12.59 (s, 1 H).

4-110 3-Cyclopentyl-2-[4-(piperazine-1-sulfonyl)-phenyl]-N-(5-piperazin-1-yl-thiazolo[5,4-b]pyridin-2-yl)-propionamide: MS M+1 585, <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ ppm 1.09 - 1.20 (m, 1 H) 1.14 (dd, *J*=14.78, 3.92 Hz, 1 H) 1.45 (dd, *J*=7.33, 4.80 Hz, 2 H) 1.52 - 1.63 (m, 1 H) 1.58 (d, *J*=7.83 Hz, 2 H) 1.76 (ddd, *J*=19.26, 7.01, 6.82 Hz, 3 H) 2.16 (d, *J*=7.07 Hz, 1 H) 3.14 (d, *J*=11.37 Hz, 11 H) 3.78 (br. s., 1 H) 3.76 (d, *J*=5.31 Hz, 3 H) 4.17 (t, *J*=7.58 Hz, 1 H) 7.06 (d, *J*=9.09 Hz, 1 H) 7.70 - 7.75 (m, 2 H) 7.75 - 7.81 (m, 2 H) 7.94 (d, *J*=9.09 Hz, 1 H) 9.05 (br. s., 1 H) 9.25 (br. s., 2 H) 12.66 (s, 1 H).

4-111 3-Cyclopentyl-N-[5-(4-methyl-piperazin-1-yl)-thiazolo[5,4-b]pyridin-2-yl]-2-[4-(piperazine-1-sulfonyl)-phenyl]-propionamide: MS M+1 599, <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ ppm 1.09 - 1.21 (m, 2 H) 1.45 (dd, *J*=7.20, 4.67 Hz, 2 H) 1.52 - 1.63 (m, 3 H) 1.76 (td, *J*=13.89, 6.82 Hz, 2 H) 1.75 (d, *J*=6.57 Hz, 1 H) 2.15 (t, *J*=7.71 Hz, 1 H) 2.80 (d, *J*=4.55 Hz, 3 H) 3.13 (br. s., 9 H) 3.28 (br. s., 2 H) 3.47 (br. s., 2 H) 4.37 (br. s., 2 H) 7.09 (d, *J*=9.09 Hz, 1 H) 7.69 - 7.75 (m, 2 H) 7.75 - 7.81 (m, 2 H) 7.95 (d, *J*=8.84 Hz, 1 H) 9.01 (br. s., 2 H) 10.85 (br. s., 1 H) 12.66 (s, 1 H).

4-112 3-Cyclopentyl-2-[4-(piperazine-1-sulfonyl)-phenyl]-N-(5-pyridin-3-yl-thiazolo[5,4-b]pyridin-2-yl)-propionamide: MS M+1 577, <sup>1</sup>H NMR (400 MHz, DMSO-*D*<sub>6</sub>) δ ppm 1.10 - 1.22 (m, 2 H) 1.45 (dd, *J*=7.33, 4.80 Hz, 2 H) 1.60 (td, *J*=15.22, 7.20 Hz, 3 H) 1.68 - 1.79 (m, 2 H) 1.79 - 1.86 (m, 1 H) 2.20 (ddd, *J*=13.20, 7.96, 7.64 Hz, 1 H) 2.67 - 2.74 (m, 4 H) 2.77

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(d,  $J=4.80$  Hz, 4 H) 4.14 (t,  $J=7.58$  Hz, 1 H) 7.53 (dd,  $J=8.08$ , 4.80 Hz, 1 H) 7.71 (q,  $J=8.76$  Hz, 4 H) 8.13 - 8.22 (m, 2 H) 8.48 (dt,  $J=8.08$ , 2.02 Hz, 1 H) 8.63 (dd,  $J=4.67$ , 1.64 Hz, 1 H) 9.30 (d,  $J=2.27$  Hz, 1 H).

4-113 3-Cyclopentyl-2-[4-(4,7-diaza-spiro[2.5]octane-7-sulfonyl)-phenyl]-N-(5-pyridin-4-yl-thiazolo[5,4-b]pyridin-2-yl)-propionamide: MS  $M+1$  603,  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  ppm 0.43 (d,  $J=7.33$  Hz, 3 H) 1.16 (br. s., 2 H) 1.24 (s, 1 H) 1.45 (dd,  $J=7.33$ , 4.55 Hz, 2 H) 1.53 - 1.65 (m, 3 H) 1.73 (br. s., 2 H) 1.82 (ddd,  $J=13.58$ , 7.07, 6.88 Hz, 1 H) 2.18 (t,  $J=7.58$  Hz, 1 H) 2.63 - 2.71 (m, 2 H) 2.72 - 2.83 (m, 4 H) 4.08 - 4.16 (m, 1 H) 7.65 - 7.74 (m, 3 H) 7.70 (d,  $J=5.31$  Hz, 3 H) 8.10 (d,  $J=6.32$  Hz, 1 H) 8.10 (d,  $J=2.78$  Hz, 1 H) 8.22 (s, 2 H) 8.70 (d,  $J=6.06$  Hz, 1 H) 8.70 (d,  $J=3.03$  Hz, 1 H).

4-114 3-Cyclopentyl-2-[4-(4-methyl-piperazine-1-sulfonyl)-phenyl]-N-(5-trifluoromethyl-thiazolo[5,4-b]pyridin-2-yl)-propionamide: MS  $MH^+$  = 582,  $^1\text{H}$  NMR (400 MHz, DMSO- $D_6$ )  $\delta$  ppm 1.15-1.30 (m, 2 H) 1.45-1.55 (m, 2 H) 1.58-1.68 (m, 3 H) 1.73 - 1.83 (m, 2 H) 1.88-1.94 (m, 1 H) 2.19 - 2.30 (m, 1 H) 2.60-2.70 (m, 2 H) 2.79 (s, 3 H) 3.12-3.33 (m, 2 H) 3.46 (s, 2 H) 3.81-3.87 (m, 2 H) 4.28 (t,  $J=7.8$  Hz, 1 H) 7.80 (d,  $J=8.3$  Hz, 2 H) 7.86 (d,  $J=8.3$  Hz, 2 H) 8.04 (d,  $J=8.4$  Hz, 1 H) 8.40 (d,  $J=8.4$  Hz, 1 H) 10.26 (broad s, 1 H)

4-115 3-Cyclopentyl-2-[4-(4-methyl-piperazine-1-sulfonyl)-phenyl]-N-[5-(tetrahydropyran-4-ylamino)-thiazolo[5,4-b]pyridin-2-yl]-propionamide MS  $MH^+$  = 613,  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  ppm 1.15 (br. s., 2 H) 1.37 - 1.48 (m, 4 H) 1.57 (br. s., 3 H) 1.78 (d,  $J=17.18$  Hz, 1 H) 1.77 (d,  $J=6.06$  Hz, 2 H) 1.88 (br. s., 2 H) 2.16 (d,  $J=12.88$  Hz, 1 H) 2.76 (s, 3 H) 3.15 (br. s., 2 H) 3.43 (t,  $J=11.24$  Hz, 5 H) 3.40 (br. s., 1 H) 3.88 (br. s., 4 H) 4.03 - 4.12 (m, 1 H) 6.58 (d,  $J=8.84$  Hz, 1 H) 7.72 (d,  $J=7.58$  Hz, 2 H) 7.68 (s, 1 H) 7.76 - 7.81 (m, 2 H) 12.40 (s, 1 H)

4-116 3-Cyclopentyl-N-[5-(4-dimethylamino-phenyl)-thiazolo[5,4-b]pyridin-2-yl]-2-[4-(4-methyl-piperazine-1-sulfonyl)-phenyl]-propionamide MS  $MH^+$  = 633,  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  ppm 1.16 (br. s., 2 H) 1.45 (dd,  $J=7.45$ , 4.93 Hz, 2 H) 1.60 (d,  $J=8.08$  Hz, 3 H) 1.75 (br. s., 1 H) 1.73 (d,  $J=3.79$  Hz, 1 H) 1.84 (d,  $J=7.07$  Hz, 1 H) 2.18 (t,  $J=7.58$  Hz, 1 H) 2.76 (s, 3 H) 2.98 (s, 6 H) 3.15 (br. s., 2 H) 3.45 (br. s., 4 H) 3.80 (br. s., 2 H) 4.16 (t,  $J=7.58$  Hz, 1 H) 6.80 (d,  $J=9.09$  Hz, 2 H) 7.72 - 7.82 (m, 4 H) 7.97 (d,  $J=8.84$  Hz, 2 H) 7.92 (d,  $J=8.59$  Hz, 1 H) 8.06 (d,  $J=8.59$  Hz, 1 H) 12.80 (s, 1 H)

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4-117 4-(2-{3-Cyclopentyl-2-[4-(4-methyl-piperazine-1-sulfonyl)-phenyl]-propionylamino}-thiazolo[5,4-b]pyridin-5-yl)-benzoic acid MS  $MH^+$  = 634,  $^1H$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  ppm 1.14 (d,  $J=6.32$  Hz, 2 H) 1.37 - 1.48 (m, 1 H) 1.43 (dd,  $J=7.33$ , 4.55 Hz, 2 H) 1.62 (d,  $J=7.33$  Hz, 1 H) 1.56 (d,  $J=2.53$  Hz, 2 H) 1.68 - 1.79 (m, 3 H) 2.10 (s, 3 H) 2.16 (dd,  $J=7.33$ , 5.81 Hz, 1 H) 2.32 (t,  $J=4.17$  Hz, 4 H) 2.87 (br. s., 4 H) 3.91 (br. s., 1 H) 7.67 (s, 4 H) 7.94 (d,  $J=8.34$  Hz, 3 H) 7.90 (s, 1 H) 8.01 - 8.07 (m, 2 H)

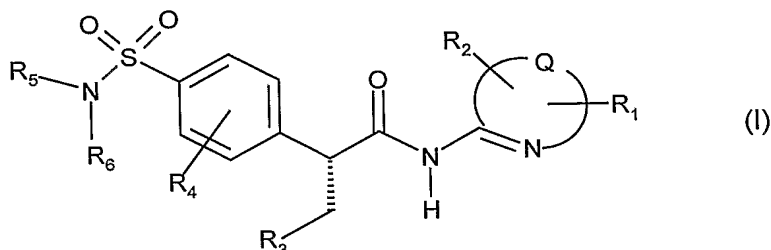
All of the U.S. patents, U.S. patent application publications, U.S. patent applications, foreign patents, foreign patent applications and non-patent publications referred to in this specification and/or listed in the Application Data Sheet are incorporated herein by reference, in their entirety.

From the foregoing it will be appreciated that, although specific embodiments of the invention have been described herein for purposes of illustration, various modifications may be made without deviating from the spirit and scope of the invention.

Accordingly, the invention is not limited except as by the appended claims.

What is claimed is:

1. A compound of the formula



wherein

Q combined together with the carbon and nitrogen atoms to which it is attached form a 5- to 6-membered monocyclic heteroaromatic ring; or

Q combined together with the carbon and nitrogen atoms to which it is attached form a 9- to 10-membered bicyclic heterocycle;

R<sub>1</sub> and R<sub>2</sub> are, independently from each other, hydrogen, halogen, cyano, nitro, optionally substituted alkyl, alkoxy, alkylthio, alkylthiono, sulfonyl, free or esterified carboxy, carbamoyl, sulfamoyl, optionally substituted amino, aryl or heterocyclyl; or

R<sub>2</sub> is absent;

R<sub>3</sub> is C<sub>3</sub>-C<sub>6</sub> cycloalkyl or C<sub>3</sub>-C<sub>6</sub> heterocyclyl;

R<sub>4</sub> is hydrogen, halogen, cyano, lower alkyl or lower alkoxy;

R<sub>5</sub> is hydrogen, optionally substituted alkyl, or cycloalkyl;

R<sub>6</sub> is -(CR<sub>7</sub>R<sub>8</sub>)<sub>m</sub>-W-R<sub>9</sub> in which

R<sub>7</sub> and R<sub>8</sub> are, independently from each other, hydrogen, optionally substituted alkyl or cycloalkyl; or

R<sub>7</sub> and R<sub>8</sub> combined are alkylene which together with the carbon atom to which they are attached form a 3- to 7-membered ring;

m is zero or an integer from 1 to 5;

W is -NR<sub>10</sub>- in which

R<sub>10</sub> is hydrogen, optionally substituted alkyl or heterocyclyl; or

R<sub>10</sub> is -C(O)R<sub>11</sub>, -C(O)OR<sub>11</sub>, or -C(O)NR<sub>12</sub>R<sub>13</sub> in which

R<sub>11</sub> and R<sub>12</sub> are, independently from each other, optionally substituted alkyl, cycloalkyl, aryl, heteroaryl, aralkyl or heteroaralkyl;

R<sub>13</sub> is hydrogen or lower alkyl; or



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$R_{13}$  and  $R_{12}$  combined are alkylene which together with the nitrogen atom to which they are attached form a 4- to 7-membered ring; or

W is absent;

$R_9$  is hydrogen, optionally substituted  $C_1$ - $C_7$  alkyl, cycloalkyl, aryl or heterocyclyl; or

$R_9$  and  $R_{10}$  combined are alkylene which together with the nitrogen atom to which they are attached form a 4- to 7-membered ring; or

$R_6$  and  $R_5$  combined are alkylene which together with the nitrogen atom to which they are attached form a 4- to 7-membered ring which may be optionally substituted, or may contain 1 to 3 other heteroatoms selected from oxygen, nitrogen and sulfur, or may be part of another ring;

or an enantiomer thereof; or an enantiomeric mixture thereof; or a pharmaceutically acceptable salt thereof.

2. A compound according to Claim 1, wherein

$R_1$  and  $R_2$  are, independently from each other, hydrogen, halogen, cyano, nitro, optionally substituted alkyl, alkoxy, alkylthio, alkylthiono, sulfonyl, free or esterified carboxy, carbamoyl, sulfamoyl, optionally substituted amino, aryl or heterocyclyl; or

$R_2$  is absent;

$R_3$  is cyclopentyl;

$R_4$  is hydrogen;

$R_5$  is hydrogen or lower alkyl;

$R_6$  is  $-(CR_7R_8)_m-W-R_9$  in which

$R_7$  and  $R_8$  are independently hydrogen or optionally substituted lower alkyl;

m is zero or an integer from 1 to 5;

W is  $-NR_{10}-$  in which

$R_{10}$  is hydrogen or lower alkyl; or

$R_{10}$  is  $-C(O)R_{11}$ ,  $-C(O)OR_{11}$ , or  $-C(O)NR_{12}R_{13}$  in which

$R_{11}$  and  $R_{12}$  are, independently from each other, optionally substituted alkyl, cycloalkyl, aryl, heteroaryl, aralkyl or heteroaralkyl;

$R_{13}$  is hydrogen or lower alkyl; or

$R_{13}$  and  $R_{12}$  combined are alkylene which together with the nitrogen atom to which they are attached form a 5- to 7-membered ring; or

W is absent;

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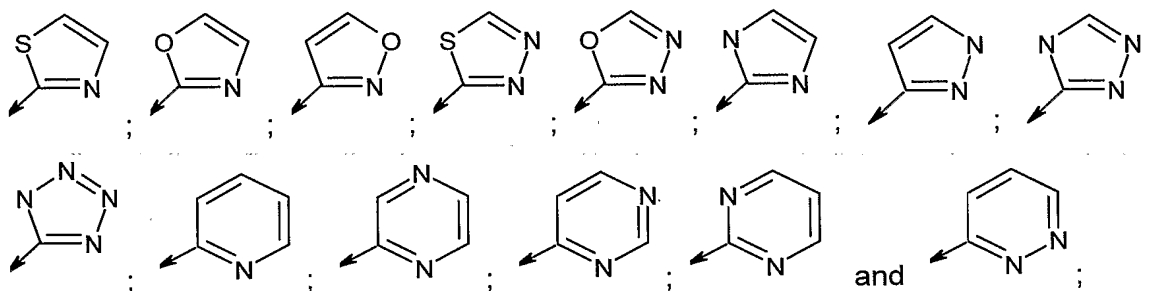
$R_9$  is hydrogen, optionally substituted  $C_1$ - $C_7$  alkyl, cycloalkyl, aryl or heterocyclyl; or  $R_9$  and  $R_{10}$  combined are alkylene which together with the nitrogen atom to which they are attached form a 5- to 7-membered ring; or

$R_6$  and  $R_5$  combined are alkylene which together with the nitrogen atom to which they are attached form a 4- to 7-membered ring which may be optionally substituted, or may contain 1 to 3 other heteroatoms selected from oxygen, nitrogen and sulfur, or may be part of another ring;

or an enantiomer thereof; or an enantiomeric mixture thereof; or a pharmaceutically acceptable salt thereof.

3. A compound according to Claim 2, wherein

Q combined together with the carbon and nitrogen atoms to which it is attached form a 5- to 6-membered monocyclic heteroaromatic ring which is selected from the group consisting of



$R_5$  is hydrogen or lower alkyl;

$R_6$  is  $-(CR_7R_8)_m-W-R_9$  in which

$R_7$  and  $R_8$  are hydrogen;

$m$  is an integer from 2 to 5;

$W$  is  $-NR_{10}-$  in which

$R_{10}$  is hydrogen or lower alkyl; or

$R_{10}$  is  $-C(O)R_{11}$ ,  $-C(O)OR_{11}$ , or  $-C(O)NR_{12}R_{13}$  in which

$R_{11}$  and  $R_{12}$  are, independently from each other, optionally substituted alkyl, cycloalkyl, aryl, heteroaryl, aralkyl or heteroaralkyl;

$R_{13}$  is hydrogen or lower alkyl; or

$R_{13}$  and  $R_{12}$  combined are alkylene which together with the nitrogen atom to which they are attached form a 5- to 7-membered ring; or

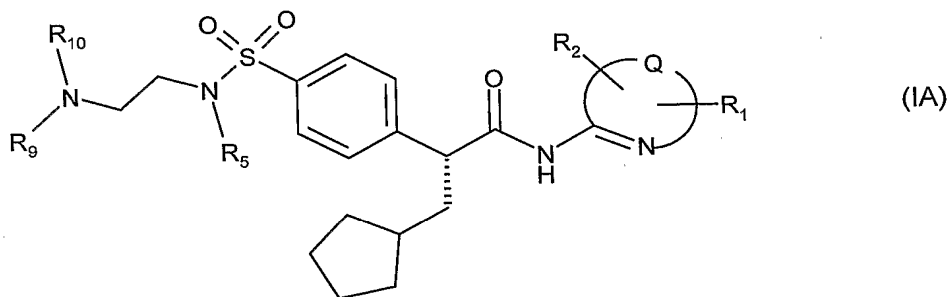
$W$  is absent;

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$R_9$  is hydrogen, optionally substituted  $C_1$ - $C_7$  alkyl, cycloalkyl, aryl or heterocyclyl; or  
 $R_9$  and  $R_{10}$  combined are alkylene which together with the nitrogen atom to which  
they are attached form a 5- to 7-membered ring;

or an enantiomer thereof; or an enantiomeric mixture thereof; or a pharmaceutically  
acceptable salt thereof.

4. A compound according to Claim 3 of the formula



wherein

$R_1$  is hydrogen, halogen, cyano, trifluoromethyl, alkoxy, alkylthio or carboxy;

$R_2$  is absent;

$R_5$  is hydrogen or lower alkyl;

$R_9$  is hydrogen, optionally substituted  $C_1$ - $C_7$  alkyl, cycloalkyl, aryl or heterocyclyl;

$R_{10}$  is hydrogen or lower alkyl; or

$R_{10}$  is  $-C(O)R_{11}$ ,  $-C(O)OR_{11}$ , or  $-C(O)NR_{12}R_{13}$  in which

$R_{11}$  and  $R_{12}$  are, independently from each other, optionally substituted alkyl,  
cycloalkyl, aryl, heteroaryl, aralkyl or heteroaralkyl;

$R_{13}$  is hydrogen or lower alkyl; or

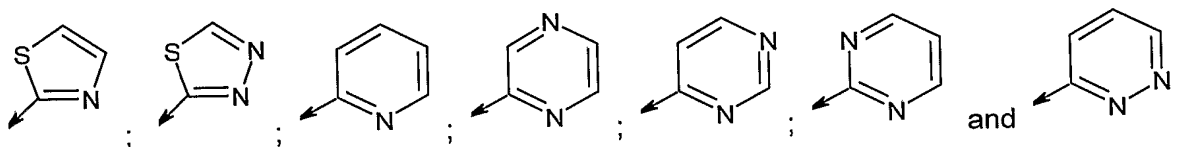
$R_{13}$  and  $R_{12}$  combined are alkylene which together with the nitrogen atom to which  
they are attached form a 5- to 7-membered ring; or

$R_{10}$  and  $R_9$  combined are alkylene which together with the nitrogen atom to which they  
are attached form a 5- to 7-membered ring;

or an enantiomer thereof; or an enantiomeric mixture thereof; or a pharmaceutically  
acceptable salt thereof.

5. A compound according to Claim 4, wherein

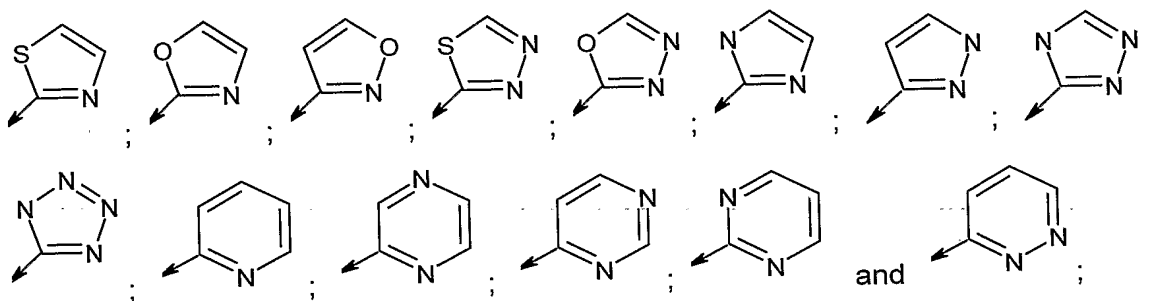
Q combined together with the carbon and nitrogen atoms to which it is attached form a 5- to 6-membered monocyclic heteroaromatic ring which is selected from the group consisting of



or an enantiomer thereof; or an enantiomeric mixture thereof; or a pharmaceutically acceptable salt thereof.

6. A compound according to Claim 2, wherein

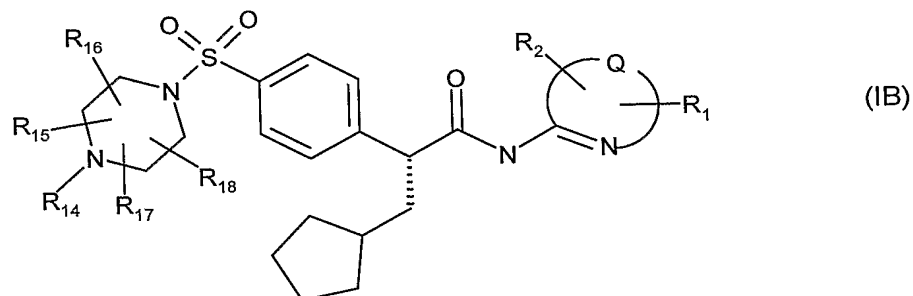
Q combined together with the carbon and nitrogen atoms to which it is attached form a 5- to 6-membered monocyclic heteroaromatic ring which is selected from the group consisting of



$R_6$  and  $R_5$  combined are alkylene which together with the nitrogen atom to which they are attached form a 4- to 7-membered ring which may be optionally substituted, or may contain 1 to 3 other heteroatoms selected from oxygen, nitrogen and sulfur, or may be part of another ring;

or an enantiomer thereof; or an enantiomeric mixture thereof; or a pharmaceutically acceptable salt thereof.

7. A compound according to Claim 6 of the formula



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wherein

$R_1$  is hydrogen, halogen, cyano, trifluoromethyl, alkoxy, alkylthio or carboxy;

$R_2$  is absent;

$R_{14}$  is hydrogen, optionally substituted lower alkyl, cycloalkyl, aryl, heteroaryl, aralkyl or heteroaralkyl; or

$R_{14}$  is  $-C(O)R_{19}$ ,  $-C(O)OR_{19}$ , or  $-C(O)NR_{20}R_{21}$  in which

$R_{19}$  and  $R_{20}$  are, independently from each other, optionally substituted alkyl, cycloalkyl, aryl, heteroaryl, aralkyl or heteroaralkyl;

$R_{21}$  is hydrogen or lower alkyl; or

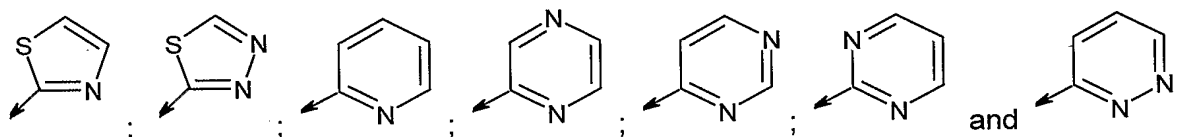
$R_{21}$  and  $R_{20}$  combined are alkylene which together with the nitrogen atom to which they are attached form a 5- to 7-membered ring;

$R_{15}$ ,  $R_{16}$ ,  $R_{17}$  and  $R_{18}$  are, independently from each other, hydrogen, halogen, hydroxy, alkoxy, free or esterified carboxy, optionally substituted lower alkyl, cycloalkyl, aryl, aralkyl, heteroaralkyl or heterocyclyl;

or an enantiomer thereof; or an enantiomeric mixture thereof; or a pharmaceutically acceptable salt thereof.

8. A compound according to Claim 7, wherein

Q combined together with the carbon and nitrogen atoms to which it is attached form a 5- to 6-membered monocyclic heteroaromatic ring which is selected from the group consisting of



or an enantiomer thereof; or an enantiomeric mixture thereof; or a pharmaceutically acceptable salt thereof.

9. A compound according to Claim 8, wherein

$R_{14}$  is methyl;

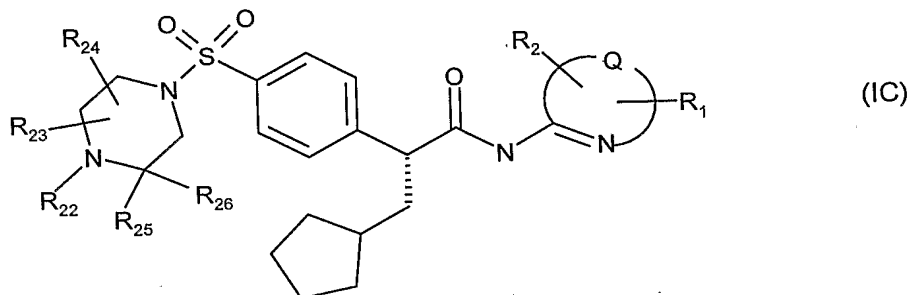
or an enantiomer thereof; or an enantiomeric mixture thereof; or a pharmaceutically acceptable salt thereof.

10. A compound according to Claim 8, wherein

$R_{14}$ ,  $R_{15}$ ,  $R_{16}$ ,  $R_{17}$  and  $R_{18}$  are, independently from each other, hydrogen or methyl;

or an enantiomer thereof; or an enantiomeric mixture thereof; or a pharmaceutically acceptable salt thereof.

11. A compound according to Claim 6 of the formula



wherein

$R_1$  is hydrogen, halogen, cyano, trifluoromethyl, alkoxy, alkylthio or carboxy;

$R_2$  is absent;

$R_{22}$  is hydrogen, optionally substituted lower alkyl, cycloalkyl, aryl, heteroaryl, aralkyl or heteroaralkyl; or

$R_{22}$  is  $-C(O)R_{19}$ ,  $-C(O)OR_{19}$ , or  $-C(O)NR_{20}R_{21}$  in which

$R_{19}$  and  $R_{20}$  are, independently from each other, optionally substituted alkyl, cycloalkyl, aryl, heteroaryl, aralkyl or heteroaralkyl;

$R_{21}$  is hydrogen or lower alkyl; or

$R_{21}$  and  $R_{20}$  combined are alkylene which together with the nitrogen atom to which they are attached form a 5- to 7-membered ring;

$R_{23}$ ,  $R_{24}$ ,  $R_{25}$  and  $R_{26}$  are, independently from each other, hydrogen, halogen, hydroxy, alkoxy, free or esterified carboxy, optionally substituted lower alkyl, cycloalkyl, aryl, aralkyl, heteroaralkyl or heterocyclyl; or

$R_{22}$  and  $R_{25}$  combined are alkylene which together with the nitrogen and carbon atoms to which they are attached form a 4- to 7-membered ring; or

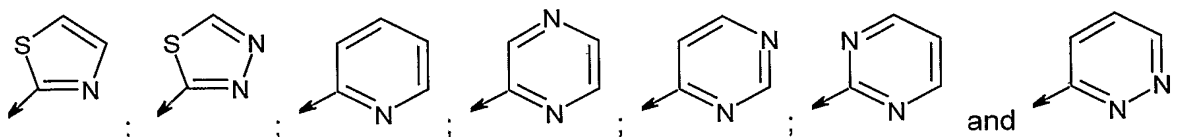
$R_{25}$  and  $R_{26}$  combined are alkylene which together with the carbon atom to which they are attached form a 3- to 7-membered ring;

or an enantiomer thereof; or an enantiomeric mixture thereof; or a pharmaceutically acceptable salt thereof.

12. A compound according to Claim 11, wherein

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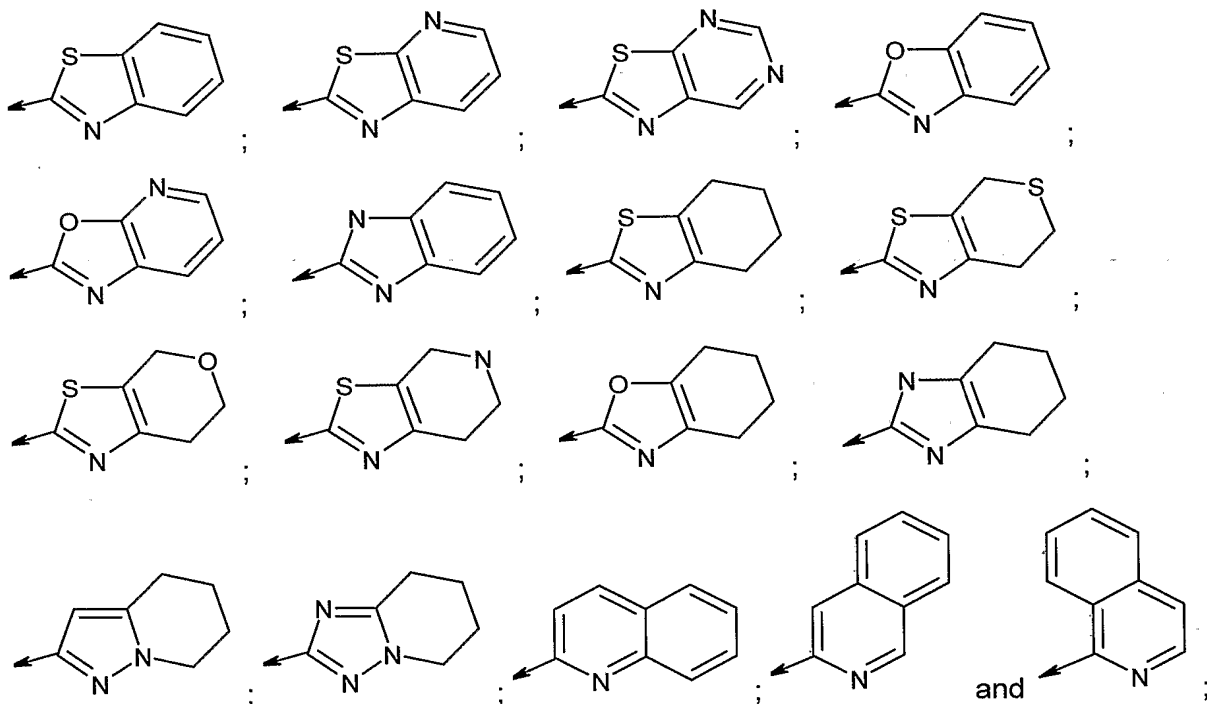
Q combined together with the carbon and nitrogen atoms to which it is attached form a 5- to 6-membered monocyclic heteroaromatic ring which is selected from the group consisting of



or an enantiomer thereof; or an enantiomeric mixture thereof; or a pharmaceutically acceptable salt thereof.

13. A compound according to Claim 2, wherein

Q combined together with the carbon and nitrogen atoms to which it is attached form a 9- to 10-membered bicyclic heterocycle which is selected from the group consisting of



$R_5$  is hydrogen or lower alkyl;

$R_6$  is  $-(CR_7R_8)_m-W-R_9$  in which

$R_7$  and  $R_8$  are hydrogen;

$m$  is an integer from 2 to 5;

$W$  is  $-NR_{10}-$  in which

$R_{10}$  is hydrogen or lower alkyl; or

$R_{10}$  is  $-C(O)R_{11}$ ,  $-C(O)OR_{11}$ , or  $-C(O)NR_{12}R_{13}$  in which

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$R_{11}$  and  $R_{12}$  are, independently from each other, optionally substituted alkyl, cycloalkyl, aryl, heteroaryl, aralkyl or heteroaralkyl;

$R_{13}$  is hydrogen or lower alkyl; or

$R_{13}$  and  $R_{12}$  combined are alkylene which together with the nitrogen atom to which they are attached form a 5- to 7-membered ring; or

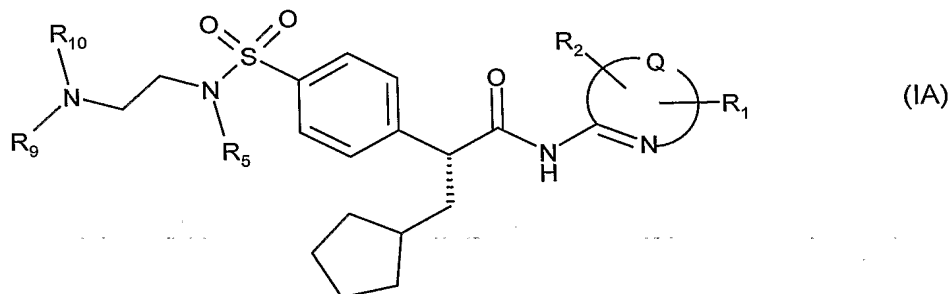
W is absent;

$R_9$  is hydrogen, optionally substituted  $C_1$ - $C_7$  alkyl, cycloalkyl, aryl or heterocyclyl; or

$R_9$  and  $R_{10}$  combined are alkylene which together with the nitrogen atom to which they are attached form a 5- to 7-membered ring;

or an enantiomer thereof; or an enantiomeric mixture thereof; or a pharmaceutically acceptable salt thereof.

14. A compound according to Claim 13 of the formula



wherein

$R_1$  is hydrogen, halogen, cyano, trifluoromethyl, alkoxy, alkylthio or carboxy;

$R_2$  is absent;

$R_5$  is hydrogen or lower alkyl;

$R_9$  is hydrogen, optionally substituted  $C_1$ - $C_7$  alkyl, cycloalkyl, aryl or heterocyclyl;

$R_{10}$  is hydrogen or lower alkyl; or

$R_{10}$  is  $-C(O)R_{11}$ ,  $-C(O)OR_{11}$ , or  $-C(O)NR_{12}R_{13}$  in which

$R_{11}$  and  $R_{12}$  are, independently from each other, optionally substituted alkyl, cycloalkyl, aryl, heteroaryl, aralkyl or heteroaralkyl;

$R_{13}$  is hydrogen or lower alkyl; or

$R_{13}$  and  $R_{12}$  combined are alkylene which together with the nitrogen atom to which they are attached form a 5- to 7-membered ring; or

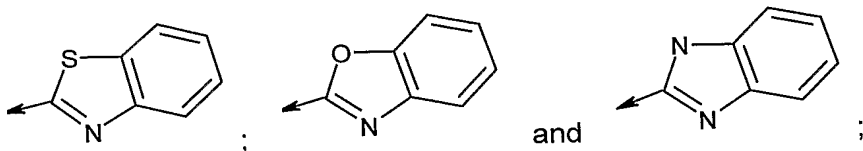
$R_{10}$  and  $R_9$  combined are alkylene which together with the nitrogen atom to which they are attached form a 5- to 7-membered ring;



or an enantiomer thereof; or an enantiomeric mixture thereof; or a pharmaceutically acceptable salt thereof.

15. A compound according to Claim 14, wherein

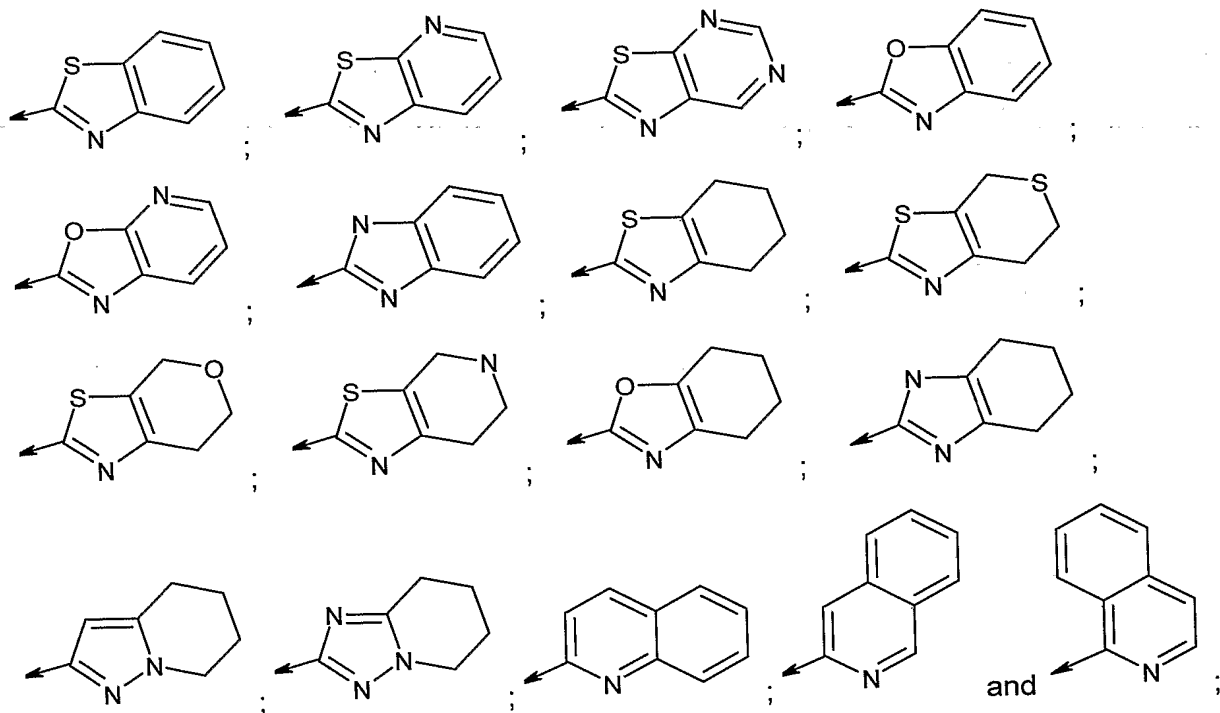
Q combined together with the carbon and nitrogen atoms to which it is attached form a 9- to 10-membered bicyclic heterocycle which is selected from the group consisting of



or an enantiomer thereof; or an enantiomeric mixture thereof; or a pharmaceutically acceptable salt thereof.

16. A compound according to Claim 2, wherein

Q combined together with the carbon and nitrogen atoms to which it is attached form a 9- to 10-membered bicyclic heterocycle which is selected from the group consisting of

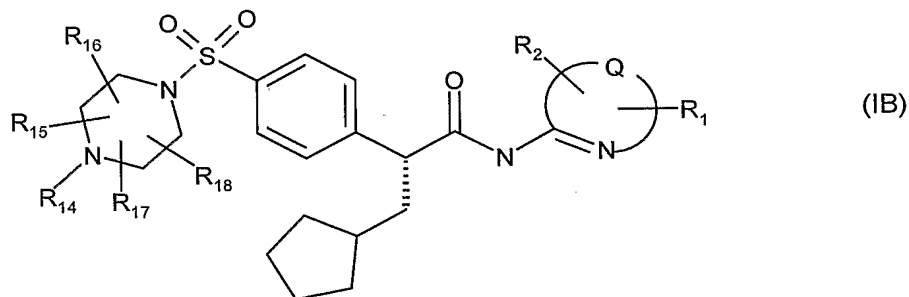


$R_6$  and  $R_5$  combined are alkylene which together with the nitrogen atom to which they are attached form a 4- to 7-membered ring which may be optionally substituted, or may contain 1 to 3 other heteroatoms selected from oxygen, nitrogen and sulfur, or may be part of another ring;

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or an enantiomer thereof; or an enantiomeric mixture thereof; or a pharmaceutically acceptable salt thereof.

17. A compound according to Claim 16 of the formula



wherein

$R_1$  is hydrogen, halogen, cyano, trifluoromethyl, alkoxy, alkylthio or carboxy;

$R_2$  is absent;

$R_{14}$  is hydrogen, optionally substituted lower alkyl, cycloalkyl, aryl, heteroaryl, aralkyl or heteroaralkyl; or

$R_{14}$  is  $-C(O)R_{19}$ ,  $-C(O)OR_{19}$ , or  $-C(O)NR_{20}R_{21}$  in which

$R_{19}$  and  $R_{20}$  are, independently from each other, optionally substituted alkyl, cycloalkyl, aryl, heteroaryl, aralkyl or heteroaralkyl;

$R_{21}$  is hydrogen or lower alkyl; or

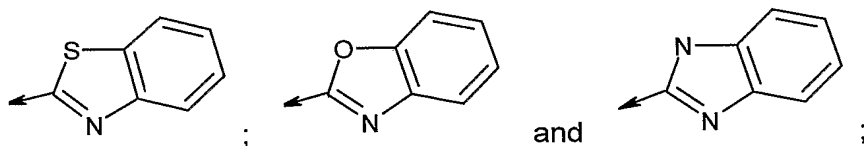
$R_{21}$  and  $R_{20}$  combined are alkylene which together with the nitrogen atom to which they are attached form a 5- to 7-membered ring;

$R_{15}$ ,  $R_{16}$ ,  $R_{17}$  and  $R_{18}$  are, independently from each other, hydrogen, halogen, hydroxy, alkoxy, free or esterified carboxy, optionally substituted lower alkyl, cycloalkyl, aryl, aralkyl, heteroaralkyl or heterocyclyl;

or an enantiomer thereof; or an enantiomeric mixture thereof; or a pharmaceutically acceptable salt thereof.

18. A compound according to Claim 17, wherein

Q combined together with the carbon and nitrogen atoms to which it is attached form a 9- to 10-membered bicyclic heterocycle which is selected from the group consisting of



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or an enantiomer thereof; or an enantiomeric mixture thereof; or a pharmaceutically acceptable salt thereof.

19. A compound according to Claim 18, wherein

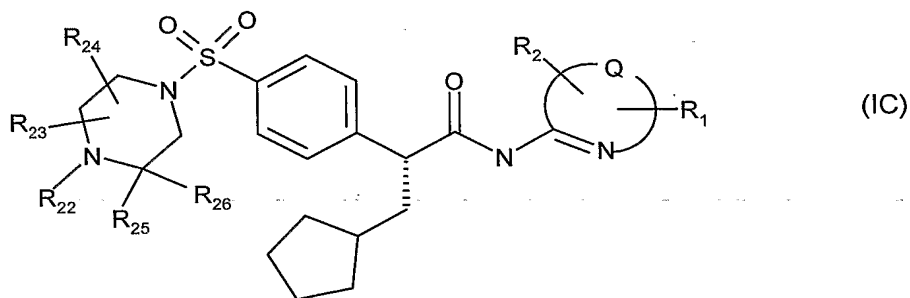
$R_{14}$  is methyl;

or an enantiomer thereof; or an enantiomeric mixture thereof; or a pharmaceutically acceptable salt thereof.

20. A compound according to Claim 18, wherein

$R_{14}$ ,  $R_{15}$ ,  $R_{16}$ ,  $R_{17}$  and  $R_{18}$  are, independently from each other, hydrogen or methyl; or an enantiomer thereof; or an enantiomeric mixture thereof; or a pharmaceutically acceptable salt thereof.

21. A compound according to Claim 16 of the formula



wherein

$R_1$  is hydrogen, halogen, cyano, trifluoromethyl, alkoxy, alkylthio or carboxy;

$R_2$  is absent;

$R_{22}$  is hydrogen, optionally substituted lower alkyl, cycloalkyl, aryl, heteroaryl, aralkyl or heteroaralkyl; or

$R_{22}$  is  $-C(O)R_{19}$ ,  $-C(O)OR_{19}$ , or  $-C(O)NR_{20}R_{21}$  in which

$R_{19}$  and  $R_{20}$  are, independently from each other, optionally substituted alkyl, cycloalkyl, aryl, heteroaryl, aralkyl or heteroaralkyl;

$R_{21}$  is hydrogen or lower alkyl; or

$R_{21}$  and  $R_{20}$  combined are alkylene which together with the nitrogen atom to which they are attached form a 5- to 7-membered ring;

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R<sub>23</sub>, R<sub>24</sub>, R<sub>25</sub> and R<sub>26</sub> are, independently from each other, hydrogen, halogen, hydroxy, alkoxy, free or esterified carboxy, optionally substituted lower alkyl, cycloalkyl, aryl, aralkyl, heteroaralkyl or heterocyclyl; or

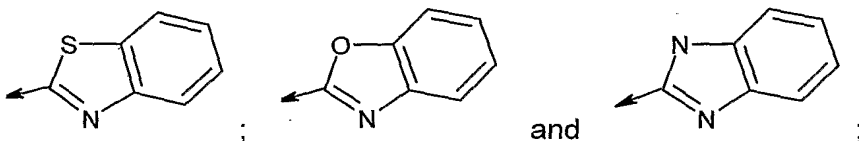
R<sub>22</sub> and R<sub>25</sub> combined are alkylene which together with the nitrogen and carbon atoms to which they are attached form a 4- to 7-membered ring; or

R<sub>25</sub> and R<sub>26</sub> combined are alkylene which together with the carbon atom to which they are attached form a 3- to 7-membered ring;

or an enantiomer thereof; or an enantiomeric mixture thereof; or a pharmaceutically acceptable salt thereof.

22. A compound according to Claim 21, wherein

Q combined together with the carbon and nitrogen atoms to which it is attached form a 9- to 10-membered bicyclic heterocycle which is selected from the group consisting of



or an enantiomer thereof; or an enantiomeric mixture thereof; or a pharmaceutically acceptable salt thereof.

23. A method for the activation of glucokinase activity in mammals which method comprises administering to a mammal, in need thereof, a therapeutically effective amount of a compound of Claim 1.

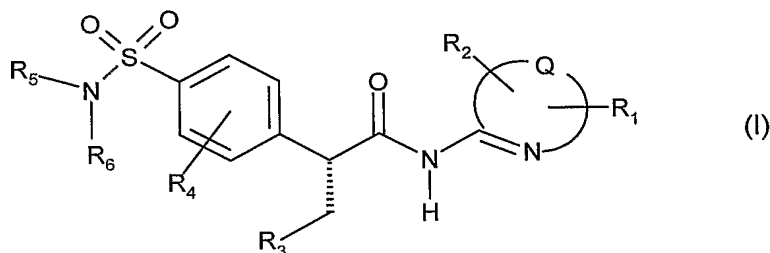
24. A method for the treatment of conditions associated with glucokinase activity in mammals which method comprises administering to a mammal, in need thereof, a therapeutically effective amount of a compound of Claim 1.

25. A method according to Claim 24, which method comprises administering a therapeutically effective amount of said compound in combination with a therapeutically effective amount of an anti-diabetic agent, a hypolipidemic agent, an anti-obesity agent or an anti-hypertensive agent.

26. A method for the treatment of impaired glucose tolerance, type 2 diabetes and obesity which method comprises administering to a mammal in need thereof a therapeutically effective amount of a compound of Claim 1.

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27. A pharmaceutical composition comprising a therapeutically effective amount of a compound of Claim 1 in combination with one or more pharmaceutically acceptable carriers.
28. A pharmaceutical composition according to Claim 27 for the treatment of impaired glucose tolerance, type 2 diabetes and obesity.
29. A pharmaceutical composition comprising a therapeutically effective amount of a compound of Claim 1 in combination with a therapeutically effective amount of an anti-diabetic agents, a hypolipidemic agent, an anti-obesity agent or an anti-hypertensive agent.
30. A pharmaceutical composition according to Claim 29 for the treatment of impaired glucose tolerance, type 2 diabetes and obesity.
31. A pharmaceutical composition according to Claim 27 or 29, for use as medicament.
32. Use of a pharmaceutical composition according to Claim 27 or 29, for the preparation of a medicament for the treatment of conditions associated with glucokinase activity.
33. Use of a compound according to Claim 1, for the preparation of a pharmaceutical composition for the treatment of conditions associated with glucokinase activity.
34. Use according to claim 32 or 33, wherein the condition associated with glucokinase activity is selected from impaired glucose tolerance, type 2 diabetes and obesity.
35. A compound according to Claim 1, for use as a medicament.
36. A compound of the formula



wherein

- Q combined together with the carbon and nitrogen atoms to which it is attached form a 5- to 6-membered monocyclic heteroaromatic ring; or
- Q combined together with the carbon and nitrogen atoms to which it is attached form a 9- to 10-membered bicyclic heterocycle;

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$R_1$  and  $R_2$  are, independently from each other, hydrogen, halogen, cyano, nitro, optionally substituted alkyl, optionally substituted alkenyl, alkynyl, alkoxy, alkylthio, alkylthiono, sulfonyl, free or esterified carboxy, carbamoyl, sulfamoyl, optionally substituted amino, aryl, aryloxy or heterocyclyl;

$R_3$  is  $C_3$ - $C_6$  cycloalkyl or  $C_3$ - $C_6$  heterocyclyl;

$R_4$  is hydrogen, halogen, cyano, lower alkyl or lower alkoxy;

$R_5$  is hydrogen, optionally substituted alkyl, or cycloalkyl;

$R_6$  is  $-(CR_7R_8)_m-W-R_9$  in which

$R_7$  and  $R_8$  are, independently from each other, hydrogen, optionally substituted alkyl or cycloalkyl; or

$R_7$  and  $R_8$  combined are alkylene which together with the carbon atom to which they are attached form a 3- to 7-membered ring;

$m$  is zero or an integer from 1 to 5;

$W$  is  $-NR_{10}-$  in which

$R_{10}$  is hydrogen, optionally substituted alkyl or heterocyclyl; or

$R_{10}$  is  $-C(O)R_{11}$ ,  $-C(O)OR_{11}$ , or  $-C(O)NR_{12}R_{13}$  in which

$R_{11}$  and  $R_{12}$  are, independently from each other, optionally substituted alkyl, cycloalkyl, aryl, heteroaryl, aralkyl or heteroaralkyl;

$R_{13}$  is hydrogen or lower alkyl; or

$R_{13}$  and  $R_{12}$  combined are alkylene which together with the nitrogen atom to which they are attached form a 4- to 7-membered ring; or

$W$  is absent;

$R_9$  is hydrogen, optionally substituted  $C_1$ - $C_7$  alkyl, cycloalkyl, aryl or heterocyclyl; or

$R_9$  and  $R_{10}$  combined are alkylene which together with the nitrogen atom to which they are attached form a 4- to 7-membered ring; or

$R_6$  and  $R_5$  combined are alkylene which together with the nitrogen atom to which they are attached form a 4- to 7-membered ring which may be optionally substituted, or may contain 1 to 3 other heteroatoms selected from oxygen, nitrogen and sulfur, or may be part of another ring;

or an enantiomer thereof; or an enantiomeric mixture thereof; or a pharmaceutically acceptable salt thereof.

37. The compound according to claim 36, wherein the compound is selected from the group consisting of:

3-Cyclopentyl-N-isoquinolin-1-yl-2-[4-(4-methyl-piperazine-1-sulfonyl)-phenyl]-propionamide;

3-Cyclopentyl-N-(1-methyl-1H-benzoimidazol-2-yl)-2-[4-(4-methyl-piperazine-1-sulfonyl)-phenyl]-propionamide;

3-Cyclopentyl-2-[4-(4-methyl-piperazine-1-sulfonyl)-phenyl]-N-[1,3,4]thiadiazol-2-yl-propionamide;

3-Cyclopentyl-2-[4-(4-methyl-piperazine-1-sulfonyl)-phenyl]-N-quinolin-2-yl-propionamide;

N-(6-Chloro-pyridazin-3-yl)-3-cyclopentyl-2-[4-(4-methyl-piperazine-1-sulfonyl)-phenyl]-propionamide;

3-Cyclopentyl-2-[4-(4-methyl-piperazine-1-sulfonyl)-phenyl]-N-(5-methyl-thiazol-2-yl)-propionamide;

2-[3-Cyclopentyl-2-[4-(4-methyl-piperazine-1-sulfonyl)-phenyl]-propionylamino]-thiazole-4-carboxylic acid;

2-[3-Cyclopentyl-2-(4-diethylsulfamoyl-phenyl)-propionylamino]-6,7-dihydro-4H-thiazolo[5,4-c]pyridine-5-carboxylic acid tert-butyl ester;

3-Cyclopentyl-2-(4-diethylsulfamoyl-phenyl)-N-(4,5,6,7-tetrahydro-thiazolo[5,4-c]pyridin-2-yl)-propionamide;

3-Cyclopentyl-2-(4-diethylsulfamoyl-phenyl)-N-(5-methyl-4,5,6,7-tetrahydro-thiazolo[5,4-c]pyridin-2-yl)-propionamide;

3-Cyclopentyl-2-(4-diethylsulfamoyl-phenyl)-N-pyrazin-2-yl-propionamide;

3-Cyclopentyl-2-(4-diethylsulfamoyl-phenyl)-N-pyridin-2-yl-propionamide;

3-Cyclopentyl-2-(4-diethylsulfamoyl-phenyl)-N-(6-trifluoromethyl-pyridin-2-yl)-propionamide;

3-Cyclopentyl-2-(4-diethylsulfamoyl-phenyl)-N-pyrimidin-2-yl-propionamide;

3-Cyclopentyl-2-(4-diethylsulfamoyl-phenyl)-N-thiazol-2-yl-propionamide;

6-[3-Cyclopentyl-2-(4-diethylsulfamoyl-phenyl)-propionylamino]-nicotinic acid;

3-Cyclopentyl-2-[4-(4-methyl-piperazine-1-sulfonyl)-phenyl]-N-(1H-tetrazol-5-yl)-propionamide;

N-(5-Chloro-thiazol-2-yl)-3-cyclopentyl-2-[4-(4-methyl-piperazine-1-sulfonyl)-phenyl]-propionamide;

3-Cyclopentyl-2-[4-(4-methyl-piperazine-1-sulfonyl)-phenyl]-N-(4-methyl-thiazol-2-yl)-propionamide;

3-Cyclopentyl-N-(1H-indazol-3-yl)-2-[4-(4-methyl-piperazine-1-sulfonyl)-phenyl]-propionamide;

3-Cyclopentyl-2-[4-(4-methyl-piperazine-1-sulfonyl)-phenyl]-N-(5-trifluoromethyl-[1,3,4]thiadiazol-2-yl)-propionamide;

N-(5-Bromo-thiazolo[5,4-b]pyridin-2-yl)-3-cyclopentyl-2-[4-(4-methyl-piperazine-1-sulfonyl)-phenyl]-propionamide;

6-{3-Cyclopentyl-2-[4-(4-methyl-piperazine-1-sulfonyl)-phenyl]-propionylamino}-nicotinic acid;

(2-{3-Cyclopentyl-2-[4-(4-methyl-piperazine-1-sulfonyl)-phenyl]-propionylamino}-thiazol-4-yl)-acetic acid ethyl ester;

N-Benzothiazol-2-yl-3-cyclopentyl-2-[4-(4-methyl-piperazine-1-sulfonyl)-phenyl]-propionamide;

N-(6-Bromo-benzothiazol-2-yl)-3-cyclopentyl-2-[4-(4-methyl-piperazine-1-sulfonyl)-phenyl]-propionamide;

3-Cyclopentyl-N-(6-methanesulfonyl-benzothiazol-2-yl)-2-[4-(4-methyl-piperazine-1-sulfonyl)-phenyl]-propionamide;

3-Cyclopentyl-2-[4-(4-methyl-piperazine-1-sulfonyl)-phenyl]-N-(5-phenoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide;

(2-{3-Cyclopentyl-2-[4-(4-methyl-piperazine-1-sulfonyl)-phenyl]-propionylamino}-thiazol-4-yl)-acetic acid;

2-{3-Cyclopentyl-2-[4-(4-methyl-piperazine-1-sulfonyl)-phenyl]-propionylamino}-benzothiazole-6-carboxylic acid ethyl ester;

2-{3-Cyclopentyl-2-[4-(4-methyl-piperazine-1-sulfonyl)-phenyl]-propionylamino}-benzothiazole-6-carboxylic acid;

2-[(R)-3-Cyclopentyl-2-[4-(4-methyl-piperazine-1-sulfonyl)-phenyl]-propionylamino]-benzothiazole-6-carboxylic acid;

2-{3-Cyclopentyl-2-[4-(4-methyl-piperazine-1-sulfonyl)-3-trifluoromethyl-phenyl]-propionylamino}-benzothiazole-6-carboxylic acid;

2-[(R)-3-Cyclopentyl-2-[4-(4-methyl-piperazine-1-sulfonyl)-phenyl]-propionylamino]-benzothiazole-6-carboxylic acid (2-methoxy-ethyl)-amide;

3-[(2-[(R)-3-Cyclopentyl-2-[4-(4-methyl-piperazine-1-sulfonyl)-phenyl]-propionylamino]-benzothiazole-6-carbonyl)-amino]-propionic acid;



3-Cyclopentyl-2-[4-(4-methyl-piperazine-1-sulfonyl)-phenyl]-N-(6-trifluoromethoxy-benzothiazol-2-yl)-propionamide;

N-(5-Chloro-thiazolo[5,4-b]pyridin-2-yl)-3-cyclopentyl-2-[4-(4-methyl-piperazine-1-sulfonyl)-phenyl]-propionamide;

(2-{3-Cyclopentyl-2-[4-(4-methyl-piperazine-1-sulfonyl)-phenyl]-propionylamino}-thiazolo[5,4-b]pyridin-5-yloxy)-acetic acid;

3-Cyclopentyl-N-(5-fluoro-thiazolo[5,4-b]pyridin-2-yl)-2-[4-(4-methyl-piperazine-1-sulfonyl)-phenyl]-propionamide;

3-Cyclopentyl-2-[4-(4-methyl-piperazine-1-sulfonyl)-phenyl]-N-(5-vinyl-thiazolo[5,4-b]pyridin-2-yl)-propionamide;

3-Cyclopentyl-N-(5-ethyl-thiazolo[5,4-b]pyridin-2-yl)-2-[4-(4-methyl-piperazine-1-sulfonyl)-phenyl]-propionamide;

3-Cyclopentyl-2-[4-(4-methyl-piperazine-1-sulfonyl)-phenyl]-N-(5-morpholin-4-yl-thiazolo[5,4-b]pyridin-2-yl)-propionamide;

3-Cyclopentyl-2-[4-(4-methyl-piperazine-1-sulfonyl)-phenyl]-N-(5-pyridin-3-yl-thiazolo[5,4-b]pyridin-2-yl)-propionamide;

3-Cyclopentyl-2-[4-(4-methyl-piperazine-1-sulfonyl)-phenyl]-N-(5-phenyl-thiazolo[5,4-b]pyridin-2-yl)-propionamide;

3-Cyclopentyl-2-[4-(4-methyl-piperazine-1-sulfonyl)-3-trifluoromethyl-phenyl]-N-(5-pyridin-4-yl-thiazolo[5,4-b]pyridin-2-yl)-propionamide;

3-Cyclopentyl-N-[5-(2-methoxy-ethoxy)-thiazolo[5,4-b]pyridin-2-yl]-2-[4-(4-methyl-piperazine-1-sulfonyl)-phenyl]-propionamide;

4-(2-{3-Cyclopentyl-2-[4-(4-methyl-piperazine-1-sulfonyl)-phenyl]-propionylamino}-thiazolo[5,4-b]pyridin-5-yloxy)-butyric acid;

3-Cyclopentyl-N-{5-[(2-methoxy-ethyl)-methyl-amino]-thiazolo[5,4-b]pyridin-2-yl}-2-[4-(4-methyl-piperazine-1-sulfonyl)-phenyl]-propionamide;

3-(2-{(R)-3-Cyclopentyl-2-[4-(4-methyl-piperazine-1-sulfonyl)-phenyl]-propionylamino}-thiazolo[5,4-b]pyridin-5-yloxy)-2,2-dimethyl-propionic acid;

3-Cyclopentyl-2-[4-(4-methyl-piperazine-1-sulfonyl)-phenyl]-N-[5-(4-methyl-piperazin-1-yl)-thiazolo[5,4-b]pyridin-2-yl]-propionamide;

3-Cyclopentyl-2-[4-(4-methyl-piperazine-1-sulfonyl)-phenyl]-N-(5-piperidin-1-yl-thiazolo[5,4-b]pyridin-2-yl)-propionamide;

2-{(R)-3-Cyclopentyl-2-[4-(4-methyl-piperazine-1-sulfonyl)-phenyl]-propionylamino}-thiazolo[5,4-b]pyridine-5-carboxylic acid (2-methoxy-ethyl)-methyl-amide

3-Cyclopentyl-N-[5-((2R,6S)-2,6-dimethyl-morpholin-4-yl)-thiazolo[5,4-b]pyridin-2-yl]-2-[4-(4-methyl-piperazine-1-sulfonyl)-phenyl]-propionamide;

3-Cyclopentyl-2-[4-(4-methyl-piperazine-1-sulfonyl)-phenyl]-N-[5-(2-methyl-pyridin-4-yl)-thiazolo[5,4-b]pyridin-2-yl]-propionamide;

3-Cyclopentyl-N-(5-ethynyl-thiazolo[5,4-b]pyridin-2-yl)-2-[4-(4-methyl-piperazine-1-sulfonyl)-phenyl]-propionamide;

3-Cyclopentyl-2-[4-(4-methyl-piperazine-1-sulfonyl)-phenyl]-N-(5-pyrimidin-5-yl-thiazolo[5,4-b]pyridin-2-yl)-propionamide;

2-{3-Cyclopentyl-2-[4-(4-methyl-piperazine-1-sulfonyl)-phenyl]-propionylamino}-thiazolo[5,4-b]pyridine-5-carboxylic acid (2-methoxy-ethyl)-amide;

2-{3-Cyclopentyl-2-[4-(4-methyl-piperazine-1-sulfonyl)-phenyl]-propionylamino}-thiazolo[5,4-b]pyridine-5-carboxylic acid dimethylamide;

3-Cyclopentyl-N-[5-(2-hydroxy-ethoxy)-thiazolo[5,4-b]pyridin-2-yl]-2-[4-(4-methyl-piperazine-1-sulfonyl)-phenyl]-propionamide;

3-Cyclopentyl-2-[4-(4-methyl-piperazine-1-sulfonyl)-phenyl]-N-(5-pyridin-4-yl-thiazolo[5,4-b]pyridin-2-yl)-propionamide;

3-Cyclopentyl-2-[4-(4-methyl-piperazine-1-sulfonyl)-phenyl]-N-[5-(morpholine-4-carbonyl)-thiazolo[5,4-b]pyridin-2-yl]-propionamide;

3-Cyclopentyl-N-(5-isopropoxy-thiazolo[5,4-b]pyridin-2-yl)-2-[4-(4-methyl-piperazine-1-sulfonyl)-phenyl]-propionamide;

N-(5-Benzyl-thiazolo[5,4-b]pyridin-2-yl)-3-cyclopentyl-2-[4-(4-methyl-piperazine-1-sulfonyl)-phenyl]-propionamide;

N-(5-Amino-thiazolo[5,4-b]pyridin-2-yl)-3-cyclopentyl-2-[4-(4-methyl-piperazine-1-sulfonyl)-phenyl]-propionamide;

3-Cyclopentyl-N-[5-(2-methoxy-ethylamino)-thiazolo[5,4-b]pyridin-2-yl]-2-[4-(4-methyl-piperazine-1-sulfonyl)-phenyl]-propionamide;

2-[3-Chloro-4-(4-methyl-piperazine-1-sulfonyl)-phenyl]-N-(5-chloro-thiazolo[5,4-b]pyridin-2-yl)-3-cyclopentyl-propionamide;

N-(5-Bromo-thiazolo[5,4-b]pyridin-2-yl)-3-cyclopentyl-2-[4-(4-methyl-piperazine-1-sulfonyl)-3-trifluoromethyl-phenyl]-propionamide;

3-Cyclopentyl-2-[4-(4-methyl-piperazine-1-sulfonyl)-3-trifluoromethyl-phenyl]-N-[5-(4-methyl-piperazin-1-yl)-thiazolo[5,4-b]pyridin-2-yl]-propionamide;

2-[3-Chloro-4-(4-methyl-piperazine-1-sulfonyl)-phenyl]-3-cyclopentyl-N-(5-pyridin-4-yl-thiazolo[5,4-b]pyridin-2-yl)-propionamide;

3-Cyclopentyl-N-[5-(2-cyclopropyl-pyridin-4-yl)-thiazolo[5,4-b]pyridin-2-yl]-2-[4-(4-methyl-piperazine-1-sulfonyl)-phenyl]-propionamide;

N-(5-Chloro-thiazolo[5,4-b]pyridin-2-yl)-3-cyclohexyl-2-[4-(4-methyl-piperazine-1-sulfonyl)-phenyl]-propionamide;

2-[3-Chloro-4-(4-methyl-piperazine-1-sulfonyl)-phenyl]-3-cyclopentyl-N-[5-(4-methyl-piperazin-1-yl)-thiazolo[5,4-b]pyridin-2-yl]-propionamide;

(S)-4-{4-[2-Cyclopentyl-1-(5-pyridin-4-yl-thiazolo[5,4-b]pyridin-2-ylcarbamoyl)-ethyl]-benzenesulfonyl}-1-methyl-piperazine-2-carboxylic acid;

3-Cyclopentyl-2-[4-((S)-3,4-dimethyl-piperazine-1-sulfonyl)-phenyl]-N-(5-pyridin-4-yl-thiazolo[5,4-b]pyridin-2-yl)-propionamide;

3-Cyclopentyl-2-[4-((S)-3,4-dimethyl-piperazine-1-sulfonyl)-phenyl]-N-(5-morpholin-4-yl-thiazolo[5,4-b]pyridin-2-yl)-propionamide;

(S)-4-{4-[2-Cyclopentyl-1-(5-pyridin-4-yl-thiazolo[5,4-b]pyridin-2-ylcarbamoyl)-ethyl]-benzenesulfonyl}-1-methyl-piperazine-2-carboxylic acid methyl ester;

(R)-4-{4-[2-Cyclopentyl-1-(5-pyridin-4-yl-thiazolo[5,4-b]pyridin-2-ylcarbamoyl)-ethyl]-benzenesulfonyl}-1-methyl-piperazine-2-carboxylic acid methyl ester;

(R)-4-{4-[2-Cyclopentyl-1-(5-pyridin-4-yl-thiazolo[5,4-b]pyridin-2-ylcarbamoyl)-ethyl]-benzenesulfonyl}-1-methyl-piperazine-2-carboxylic acid;

2-((R)-3-Cyclopentyl-2-[4-(2-methoxy-ethylsulfamoyl)-phenyl]-propionylamino)-benzothiazole-6-carboxylic acid;

2-((R)-3-Cyclopentyl-2-{4-[(2-methoxy-ethyl)-methyl-sulfamoyl]-phenyl}-propionylamino)-benzothiazole-6-carboxylic acid;

(R)-N-(5-Chloro-thiazolo[5,4-b]pyridin-2-yl)-3-cyclopentyl-2-[4-(2-methoxy-ethylsulfamoyl)-phenyl]-propionamide;

N-(5-Bromo-thiazolo[5,4-b]pyridin-2-yl)-3-cyclopentyl-2-[4-(4-methyl-4,7-diaza-spiro[2.5]octane-7-sulfonyl)-phenyl]-propionamide;

3-Cyclopentyl-2-[4-(4-methyl-4,7-diaza-spiro[2.5]octane-7-sulfonyl)-phenyl]-N-(5-pyridin-4-yl-thiazolo[5,4-b]pyridin-2-yl)-propionamide;

3-Cyclopentyl-2-[4-(4-methyl-4,7-diaza-spiro[2.5]octane-7-sulfonyl)-phenyl]-N-[5-(4-methyl-piperazin-1-yl)-thiazolo[5,4-b]pyridin-2-yl]-propionamide;

(R)-3-Cyclopentyl-2-[4-(4-methyl-4,7-diaza-spiro[2.5]octane-7-sulfonyl)-phenyl]-N-(5-pyridin-4-yl-thiazolo[5,4-b]pyridin-2-yl)-propionamide;

3-Cyclopentyl-N-(5-pyridin-4-yl-thiazolo[5,4-b]pyridin-2-yl)-2-[4-(3,3,4-trimethyl-piperazine-1-sulfonyl)-phenyl]-propionamide;

2-(4-Butyrylsulfamoyl-phenyl)-3-cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide;

3-Cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-2-{4-[4-(2-oxo-2-piperidin-1-yl-ethyl)-piperazine-1-sulfonyl]-phenyl}-propionamide;

3-Cyclopentyl-2-{4-[4-(isopropylcarbamoyl-methyl)-piperazine-1-sulfonyl]-phenyl}-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide;

1-{4-[2-Cyclopentyl-1-(5-methoxy-thiazolo[5,4-b]pyridin-2-ylcarbamoyl)-ethyl]-benzenesulfonyl}-piperidine-4-carboxylic acid;

1-{4-[2-Cyclopentyl-1-(5-methoxy-thiazolo[5,4-b]pyridin-2-ylcarbamoyl)-ethyl]-benzenesulfonyl}-piperidine-3-carboxylic acid;

((S)-1-{4-[2-Cyclopentyl-1-(5-methoxy-thiazolo[5,4-b]pyridin-2-ylcarbamoyl)-ethyl]-benzenesulfonyl}-pyrrolidin-2-yl)-acetic acid;

4-{4-[2-Cyclopentyl-1-(5-methoxy-thiazolo[5,4-b]pyridin-2-ylcarbamoyl)-ethyl]-benzenesulfonyl}-piperazine-2-carboxylic acid;

1-{4-[2-Cyclopentyl-1-(5-methoxy-thiazolo[5,4-b]pyridin-2-ylcarbamoyl)-ethyl]-benzenesulfonyl}-4-methyl-piperazine-2-carboxylic acid;

1-{4-[2-Cyclopentyl-1-(5-methoxy-thiazolo[5,4-b]pyridin-2-ylcarbamoyl)-ethyl]-benzenesulfonyl}-piperazine-2-carboxylic acid;

1-{4-[2-Cyclopentyl-1-(5-methoxy-thiazolo[5,4-b]pyridin-2-ylcarbamoyl)-ethyl]-benzenesulfonyl}-pyrrolidine-3-carboxylic acid;

4-{4-[2-Cyclopentyl-1-(5-methoxy-thiazolo[5,4-b]pyridin-2-ylcarbamoyl)-ethyl]-benzenesulfonyl}-1-methyl-piperazine-2-carboxylic acid;

{2-[3-Cyclopentyl-2-(4-diethylsulfamoyl-phenyl)-propionylamino]-thiazolo[5,4-b]pyridin-5-yloxy}-acetic acid;

N-(5-Carbamoylmethoxy-thiazolo[5,4-b]pyridin-2-yl)-3-cyclopentyl-2-(4-diethylsulfamoyl-phenyl)-propionamide;

3-(4-{4-[2-Cyclopentyl-1-(5-methoxy-thiazolo[5,4-b]pyridin-2-ylcarbamoyl)-ethyl]-benzenesulfonylamino}-piperidin-1-yl)-propionic acid;

(R)-1-{4-[2-Cyclopentyl-1-(5-methoxy-thiazolo[5,4-b]pyridin-2-ylcarbamoyl)-ethyl]-benzenesulfonyl}-piperidine-2-carboxylic acid;

(S)-1-{4-[2-Cyclopentyl-1-(5-methoxy-thiazolo[5,4-b]pyridin-2-ylcarbamoyl)-ethyl]-benzenesulfonyl}-piperidine-2-carboxylic acid;

3-(4-{4-[2-Cyclopentyl-1-(5-methoxy-thiazolo[5,4-b]pyridin-2-ylcarbamoyl)-ethyl]-benzenesulfonyl}-piperazin-1-yl)-propionic acid;

4-(4-{4-[2-Cyclopentyl-1-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)carbamoyl]-ethyl}-benzenesulfonyl)-piperazin-1-yl)-4-oxo-butyrac acid;

3-Cyclopentyl-2-[4-((S)-3-methyl-piperazine-1-sulfonyl)-phenyl]-N-(5-morpholin-4-yl-thiazolo[5,4-b]pyridin-2-yl)-propionamide;

3-Cyclopentyl-2-[4-((S)-3-methyl-piperazine-1-sulfonyl)-phenyl]-N-(5-pyridin-4-yl-thiazolo[5,4-b]pyridin-2-yl)-propionamide;

3-Cyclopentyl-N-[5-(2-methoxy-ethylamino)-thiazolo[5,4-b]pyridin-2-yl]-2-[4-(piperazine-1-sulfonyl)-phenyl]-propionamide;

3-Cyclopentyl-2-[4-(piperazine-1-sulfonyl)-phenyl]-N-(5-vinyl-thiazolo[5,4-b]pyridin-2-yl)-propionamide;

3-Cyclopentyl-2-[4-(piperazine-1-sulfonyl)-phenyl]-N-(5-pyridin-4-yl-thiazolo[5,4-b]pyridin-2-yl)-propionamide;

3-Cyclopentyl-N-(5-morpholin-4-yl-thiazolo[5,4-b]pyridin-2-yl)-2-[4-(piperazine-1-sulfonyl)-phenyl]-propionamide;

3-Cyclopentyl-2-[4-(piperazine-1-sulfonyl)-phenyl]-N-(5-piperazin-1-yl-thiazolo[5,4-b]pyridin-2-yl)-propionamide;

3-Cyclopentyl-N-[5-(4-methyl-piperazin-1-yl)-thiazolo[5,4-b]pyridin-2-yl]-2-[4-(piperazine-1-sulfonyl)-phenyl]-propionamide;

3-Cyclopentyl-2-[4-(piperazine-1-sulfonyl)-phenyl]-N-(5-pyridin-3-yl-thiazolo[5,4-b]pyridin-2-yl)-propionamide;

3-Cyclopentyl-2-[4-(4,7-diaza-spiro[2.5]octane-7-sulfonyl)-phenyl]-N-(5-pyridin-4-yl-thiazolo[5,4-b]pyridin-2-yl)-propionamide.